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# Management of Rotator Cuff Pathology

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## **Declaration**

---

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been compiled solely by me and has not been submitted in any previous application for any degree.

My academic supervisors for the PhD were:

1. Prof Damian Griffin – throughout the study period
2. Mr Christopher Smith – was a clinical lecturer at Warwick who supervised the whole of the ultrasound study and the protocol and ethics application for the microvascularity study before he moved to Exeter.
3. Prof Charles Hutchinson – replaced Christopher Smith and supervised the conduct of the microvascularity study and thesis writing until submission.

The work presented (including data generated and data analysis) was carried out by me except in the cases outlined below:

Chapter 3: The laser doppler probe placements during intraoperative blood flow measurements were done by the operating surgeons Mr Drew and Mr Lawrence and data was collected by candidate. Dr Nicholas Parsons advised on statistics.

Chapter 4: The ultrasonography protocol was written with the help of Dr Rai (Consultant Musculoskeletal Radiologist). Shoulder assessment and measurements were made by Dr Rai and Dr Wellings in the presence of the candidate who collected the data. Statistical advice given by Dr Helen Parsons

Chapter 5: Dr Nicholas Parsons provided support on statistics and the subacromial injection was administered by Mr Drew

## **Abbreviations**

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ACJ	Acromio Clavicular Joint
ACL	Anterior Cruciate Ligament
AHD	Acromio Humeral Distance
ANOVA	Analysis of Variance
AP	Antero Posterior
ASAD	Arthroscopic Subacromial Decompression
BCF	Blood Cell Flux
BMI	Body Mass Index
BSRCT	Bursal-sided Rotator Cuff Tear
CEUS	Contrast Enhanced Ultra Sonography
CI	Confidence Interval
COX	Cyclooxygenase
CSS	Constant Shoulder Score
CT	Computerised Tomography
DASH	Disability of the Arm, Shoulder and Hand
GCP	Good Clinical Practice
HDL	High Density Lipoprotein
IL	Interleukin
IQR	Inter Quartile Range
ISP	Infraspinatus
LCD	Liquid Crystal Display
LDF	Lase Doppler Flowmetry
LDL	Low Density Lipoprotein

MRA	Magnetic Resonance Arthrography
MRI	Magnetic Resonance Imaging
MTJ	Musculo Tendinous Junction
NHS	National Health Service
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OSS	Oxford Shoulder Score
OTJ	Osseo Tendinous Junction
PC	Personal Computer
PRP	Platelet Rich Plasma
RCT	Randomised Controlled trial
ROI	Regions of Interest
SAD	Subacromial Decompression
SASD	Subacromial Sub Deltoid
SC	Subscapularis
SLAP	Superior Labrum Antero Posterior
SSP	Supraspinatus
TM	Teres Minor
UHCW	University Hospitals Coventry and Warwickshire
UK	United Kingdom
USB	Universal Serial Bus
USG	Ultrasonography

## **Abstract**

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The rotator cuff refers to a group of four muscles, which arise from the scapula and insert into the head of humerus forming a cuff around the shoulder joint. They contribute to shoulder movements and provide dynamic stability at the shoulder joint. Pathology of the rotator cuff is the commonest cause for shoulder pain and its severity can vary from subacromial impingement to full thickness tears. NSAIDs and corticosteroids are two of the commonest group of drugs used in treating subacromial impingement syndrome but with conflicting evidence about their relative efficacy and risk of complications. I explored the efficacy of a subacromial NSAID (Tenoxicam) injection in a double blind randomised controlled trial but found it to be less effective compared to a subacromial corticosteroid injection as measured by functional shoulder scores at six weeks.

During the trial, I recognised that there were unresolved challenges in using Ultrasonography to diagnose rotator cuff pathology especially in differentiating between partial and full thickness tears. In this thesis, I have presented the normal ultrasound dimensions of the rotator cuff in asymptomatic young adults under the age of forty years, which has not been documented before. The study showed that the measurements are significantly different between men and women but not between dominant and non-dominant arms, suggesting that in every individual the contralateral shoulder can be used as a control, especially where the diagnosis is uncertain. Exploration of factors associated with the pathogenesis of rotator cuff tendinopathy showed that a critical zone of hypoperfusion in the supraspinatus tendon could be a factor but the evidence for it has been contradictory. An observational study presented in this thesis describes the microvascular blood flow in normal and a spectrum of pathological rotator cuffs (subacromial impingement, partial thickness tears and full thickness tears) using Laser Doppler Flowmetry in patients undergoing arthroscopic shoulder surgery. The study showed variations in microvascular blood flow in normal rotator cuffs but no evidence of a “critical zone”. Blood flow was found to be significantly lower in all groups of pathological rotator cuffs.

## **Research training**

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I have undertaken the following training during the period of my study

1. Postgraduate module on Understanding Research and Critical Appraisal in Healthcare (UReCA) – University of Warwick
2. Postgraduate module on Epidemiology and Statistics – University of Warwick
3. Good clinical practice (GCP) training – University of Warwick
4. University of Warwick Research Student Skills Programme
  - a. Practical research skills
  - b. Academic writing series
5. EndNote X4 - An Overview for Complete Beginners
6. IBM® SPSS® Statistics 22

I have attended the following conferences during my period of study

1. British Elbow and Shoulder Surgeons Annual meeting at Torquay, UK
2. British Elbow and Shoulder Surgeons Annual meeting at Leicester, UK
3. A Rotator Cuff Masterclass – Discussion and Debate, Liverpool, UK

## Research Outputs

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Parts of this thesis have already been published:

1. Karthikeyan S, Kwong HT, Upadhyay PK, Parsons N, Drew SJ, Griffin D: A double blind randomised controlled study comparing subacromial injection of tenoxicam or methylprednisolone in patients with subacromial impingement. Published in J Bone Joint Surg Br. 2010 Jan;92(1):77-82. doi: <http://dx.doi.org/10.1302/0301-620X.92B1.22137>
2. Modi CS, Smith CD, Ho K, Karthikeyan S, Rai S, Boer R, Drew SJ: Accuracy of high-resolution ultrasonography in the diagnosis of articular-sided partial thickness rotator cuff tears. Published in Shoulder and Elbow 2010 Oct;2(4):267-270 doi: <http://dx.doi.org/10.1111/j.1758-5740.2010.00088.x>
3. Karthikeyan S, Rai SB, Parsons H, Drew SD, Smith CD, Griffin DR: Ultrasound dimensions of the rotator cuff in young healthy adults. Published in J Shoulder Elbow Surg. 2014 Aug 23(8):1107-1112. doi: <http://dx.doi.org/10.1016/j.jse.2013.11.012>
4. Karthikeyan S, Griffin DR, Parsons N, Lawrence TL, Modi CS, Drew SJ, Smith CD: Microvascular blood flow in normal and pathological rotator cuffs. Published in J Shoulder Elbow Surg. 2015 Dec;24(12):1954-60. doi: <http://dx.doi.org/10.1016/j.jse.2015.07.014>

### **Publication related to his thesis**

1. Modi CS, Karthikeyan S, Marks A, Saithna A, Smith CD, Rai SB, Drew SJ:  
Accuracy of Abduction-External Rotation MRA versus Standard MRA in  
the diagnosis of Intra-Articular Shoulder Pathology.  
Published in Orthopedics. 2013 Mar 1;36(3): e337-42.  
doi: <http://dx.doi.org/10.3928/01477447-20130222-23>

As part of this thesis, I have presented the work at the following conferences

1. Microvascular blood flow in normal and pathological rotator cuff.  
British Elbow and Shoulder Society 2013 Leicester 19th June 2013
2. The normal ultrasound dimensions of the rotator cuff in healthy young  
adults. British Elbow and Shoulder Society 2012 Torquay 15th June 2012

## **Preface**

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As an orthopaedic trainee, I was interested to learn about evidence based practice and was delighted when I got the opportunity to work with Prof Griffin and Mr Drew at Warwick Medical School and the University Hospitals of Coventry and Warwickshire NHS Trust. I initially registered for MSc (by research) at Warwick Medical School and as part of it I conducted a double blind randomised control trial to compare the efficacy of subacromial injection of a Non-Steroidal Anti-Inflammatory drug with a corticosteroid in the management of subacromial impingement syndrome. During the course of the study I developed an interest in exploring further issues related to the rotator cuff, as well as factors associated with its pathology. I was encouraged to upgrade my research degree from MSc to PhD and with the support of my supervisors I successfully presented my ideas to an upgrade panel at the university and registered for a PhD.

I conducted two further studies – one looking at the ultrasound dimensions of the rotator cuff muscles and tendons in asymptomatic volunteers under the age of forty and the other measuring the microvascular blood flow of the supraspinatus tendon in normal and pathological rotator cuffs using a laser Doppler probe intra-operatively. These studies are presented in the thesis in the order they were conducted.

## Chapter 1 Introduction and Anatomy

### Summary:

*In this chapter, I will talk about the socioeconomic burden of rotator cuff problems, the anatomy of shoulder joint and the rotator cuff muscles including its vascularity. I will also outline the structure of tendons, in particular the supraspinatus.*

### Declarations:

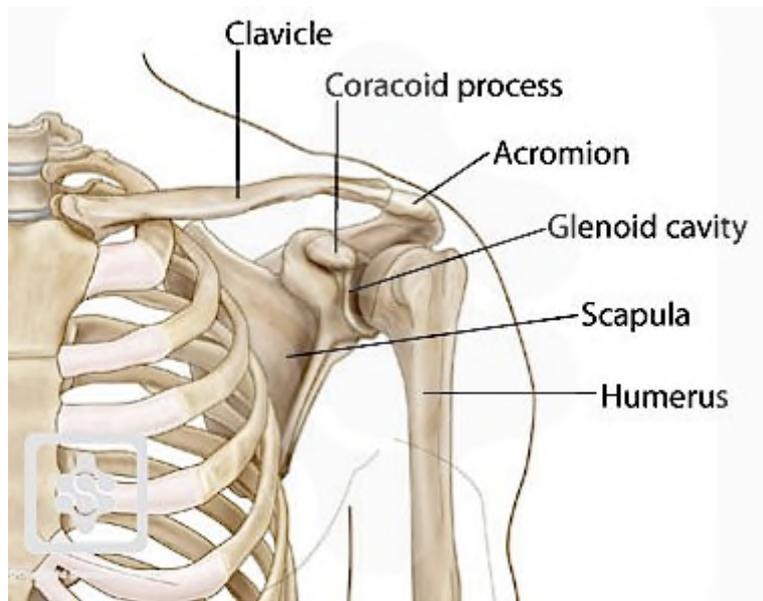
*None*

## 1.1 Introduction

Shoulder pain is the second most prevalent cause of musculoskeletal pain in the community, behind only low back pain<sup>1</sup> and can cause significant morbidity and disability<sup>2</sup>. It has been estimated that the annual incidence of shoulder pain in adults over the age of 45 years, is in excess of 1%<sup>3</sup> and self-reported prevalence lies between 16 and 26% in population studies<sup>4,5</sup>. Rotator cuff pathology is the commonest cause for painful shoulder accounting for up to 70% of cases with the supraspinatus tendon being the most commonly affected<sup>4,6,7</sup>. Rotator cuff disorders can affect adult patients of all ages and activity levels<sup>6,8</sup>. Individuals who subject their shoulders to repeat stresses as well as middle-aged and elderly persons are more commonly affected can lead to prolonged periods off work and much longer abstinence from sporting activities<sup>1</sup>. Neer has shown that the critical area for wear is centred on the supraspinatus tendon<sup>9</sup>. Only 2% of rotator cuff tears predominantly or exclusively involve the subscapularis tendon<sup>10</sup>.

## 1.2 Shoulder (Glenohumeral) joint

The glenohumeral joint, commonly called the shoulder joint is a synovial, multiaxial spheroidal joint formed by the articulation between the shallow glenoid fossa on the anterolateral surface of the scapula and the hemispherical head of the humerus. It forms the connection between the shoulder girdle and the upper limb (Figure 1-1).



**Figure 1-1: Articulations of the shoulder joint (source: [www.shoulderdoonline.co.uk](http://www.shoulderdoonline.co.uk))**

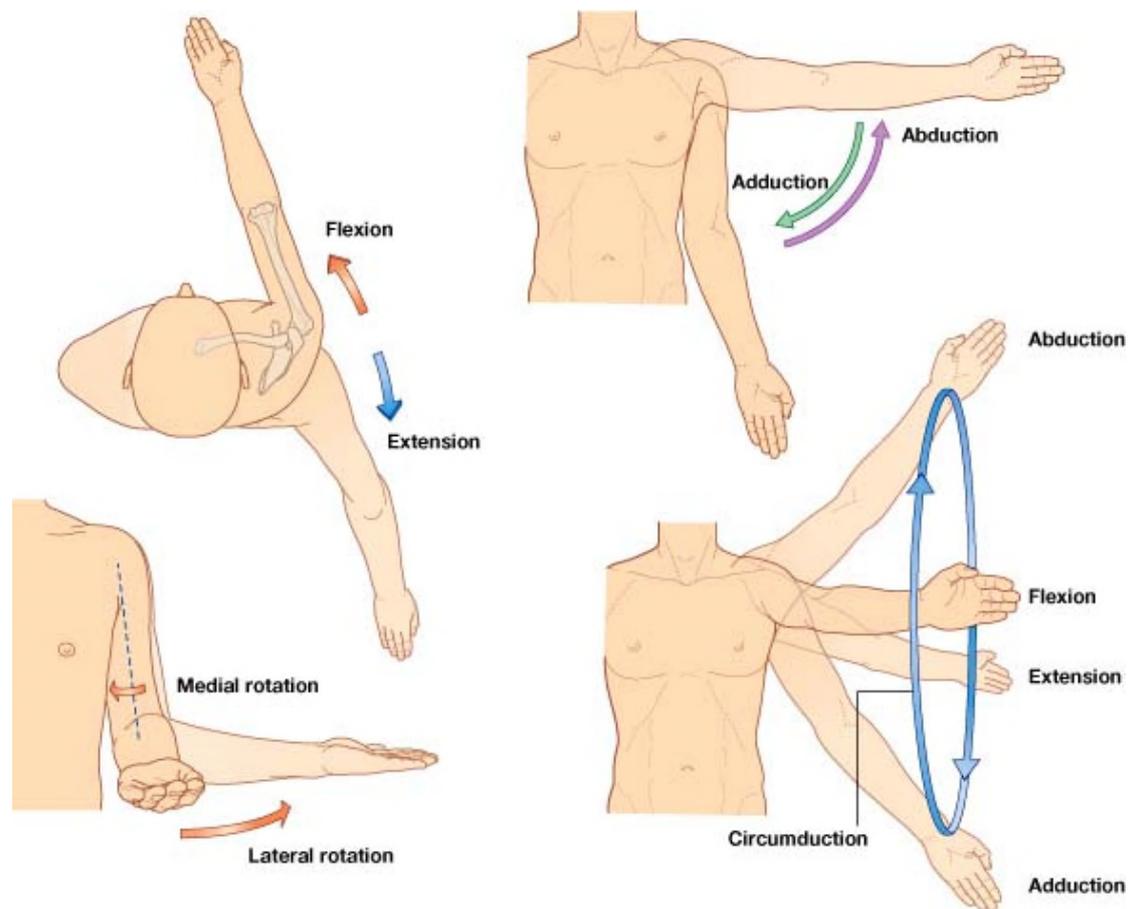
In the human embryo, by about the eighth week of gestation, the musculature of the upper limb is clearly defined and the shoulder joint takes the form of the adult glenohumeral joint<sup>11</sup>. It is the most mobile joint in the body allowing movements around three mutually perpendicular axes related to the plane of the scapula (The scapular plane is anteriorly rotated about 30° in relation to the coronal plane).

These are

1. Flexion and Extension on the sagittal plane
2. Abduction and Adduction on the coronal plane
3. Medial and Lateral rotation on the transverse plane.

These movements can occur in sequence or in combinations to produce an infinite variety of additional movements (Figure 1-2). The ball and socket joint with its shallow glenoid cavity and relative absence of bony constraint gives the shoulder a much greater range of movement than the hip but makes it inherently more unstable. Static and dynamic stability of the shoulder joint therefore

depends mostly on the surrounding muscular and soft tissue envelope, which includes the glenoid labrum, the capsule, ligaments and the rotator cuff.



**Figure 1-2: Range of shoulder movements (Source: [www.bestperformancegroup.com](http://www.bestperformancegroup.com))**

The glenoid labrum is a fibro cartilaginous rim, which goes around and deepens the glenoid fossa. A fibrous capsule lined by synovial membrane surrounds the glenohumeral joint. Medially, the capsule is attached to the glenoid margin outside the glenoid labrum. Laterally, it is attached to the anatomical neck of the humerus near the articular margin. The capsule is very lax permitting a wide range of movement at the glenohumeral joint. Three glenohumeral ligaments (superior, middle and inferior), coracohumeral ligament and the transverse humeral ligament support the glenohumeral joint. They are important stabilisers in the anterior and inferior directions.

### 1.3 Acromioclavicular joint

The acromioclavicular joint is a synovial plane joint. It is formed between the acromial (lateral) end of the clavicle and the medial acromial margin (Figure 1-1). Both surfaces are covered by fibrocartilage. The joint is surrounded by a fibrous capsule, which has a synovial lining. Two ligaments – the acromioclavicular ligament and the coracoclavicular ligament contribute to its stability. The coracoacromial arch is made up of the anterior under surface of the acromion and the coracoacromial ligament. It forms a smooth concave surface for gliding of the rotator cuff tendons during shoulder movements.

### 1.4 Rotator cuff

The term “rotator cuff” refers to a group of four muscles and their tendons that arise from the scapula and fuse to form a common insertion on the tuberosities of the humerus forming a “cuff” at the shoulder joint<sup>12</sup> (Figure 1-3, Figure 1-4). These are the subscapularis (anteriorly), supraspinatus (superiorly), infraspinatus and teres minor (posteriorly) as described in Table 1-1. The tendon of the long head of biceps is closely related to the rotator cuff. The rotator cuff inserts as a broad, continuous, multi-layered and interwoven structure onto the humeral tuberosities<sup>12</sup>.

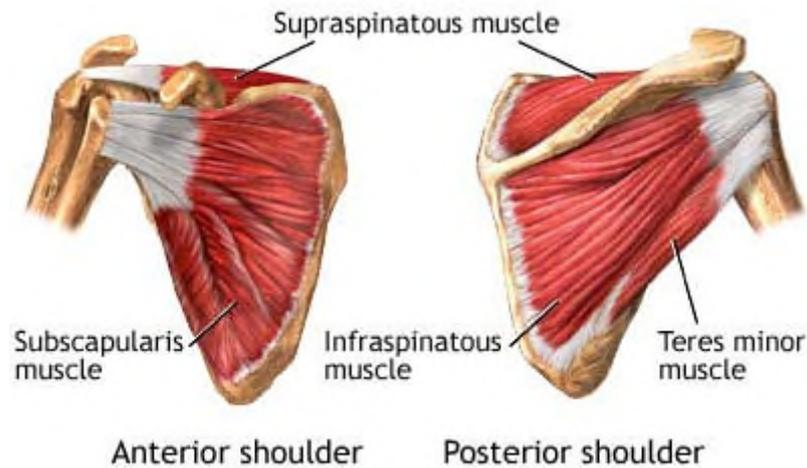


Figure 1-3: Rotator cuff muscles (source: [www.thedoctorweighsin.com](http://www.thedoctorweighsin.com))

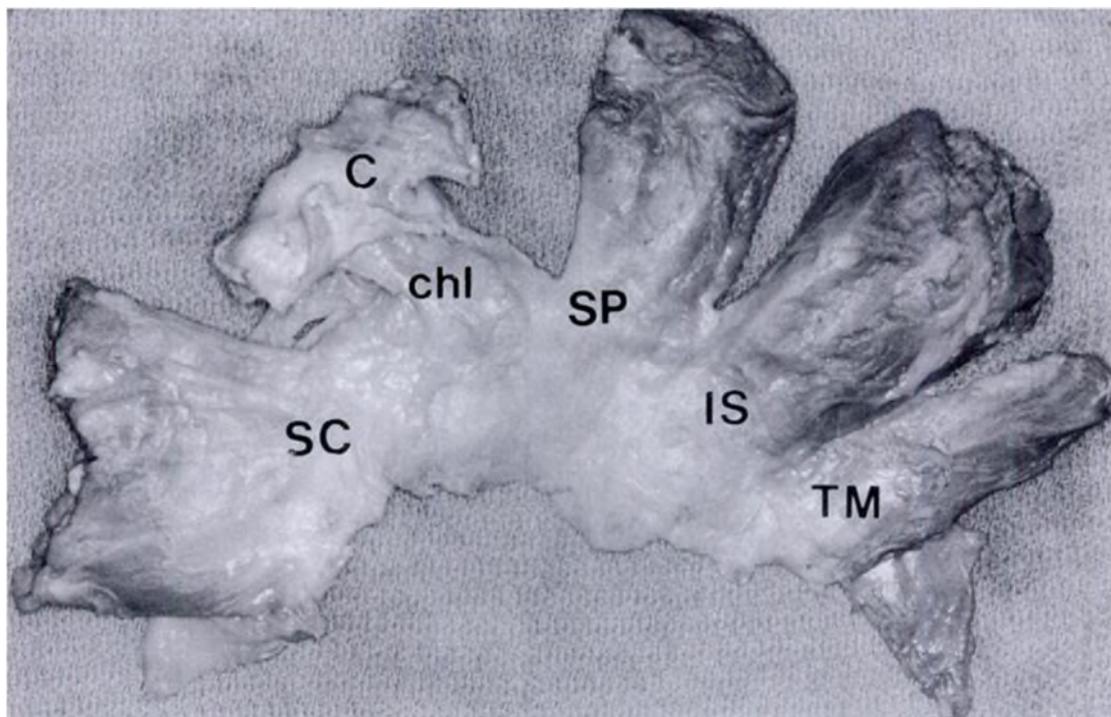


Figure 1-4: Rotator cuff insertion showing the subscapularis (SC), the osteotomized coracoid process (C) with the attached coracohumeral ligament (chl), the supraspinatus (SP), infraspinatus (IS) and teres minor (TM). (source: Clark and Harryman<sup>12</sup>)

#### 1.4.1 Musculature

The subscapularis, a triangular multipennate muscle, arises from the subscapularis fossa on the anterior surface of the scapula, and converges into a broad tendon which inserts into the lesser tuberosity of the humerus (Figure 1-3). Superiorly, the supraspinatus arises from the supraspinous fossa of the

scapula and inserts into the superior facet and the anterior portion of the middle facet of the greater tuberosity on the humeral head<sup>13,14</sup>(Figure 1-5). The supraspinatus has a distinct anterior and posterior part<sup>15</sup>. The anterior portion is thicker and more robust than the wider and thinner posterior portion<sup>15</sup>. The infraspinatus muscle occupies the infraspinatus fossa below the spine of scapula on its posterior surface, while the teres minor arises from the upper two-thirds of the axillary border of the scapula. The infraspinatus tendon inserts into the middle facet and the smaller teres minor tendon inserts into the inferior facet of the greater tuberosity on the humeral head<sup>13,14</sup> (Figure 1-6). The posterior fibres of the supraspinatus interdigitate with the anterior fibres of the infraspinatus and the two tendons cannot be easily distinguished close to their insertions in the greater tuberosity<sup>13,15</sup>. The tendons splay and interdigitate with each other leading to a wide and continuous insertion of the cuff on the tuberosities, which improve its resistance to failure under load<sup>12</sup>.

<b>Muscle</b>	<b>Origin in scapula</b>	<b>Insertion in Humerus</b>	<b>Function</b>	<b>Nerve supply</b>
<b>Subscapularis</b>	Subscapularis fossa	Lesser tuberosity	Internal rotation	Upper and lower subscapular nerves (C5, 6)
<b>Supraspinatus</b>	Supraspinous fossa	Greater tuberosity	Initiate abduction	Suprascapular nerve (C5, 6)
<b>Infraspinatus</b>	Infraspinous fossa	Greater tuberosity	External rotation	Suprascapular nerve (C5, 6)
<b>Teres Minor</b>	Lateral border	Greater tuberosity	External rotation, adduction	Axillary nerve (C5, 6)

**Table 1-1: Origin, Insertion and Function of the rotator cuff muscles**

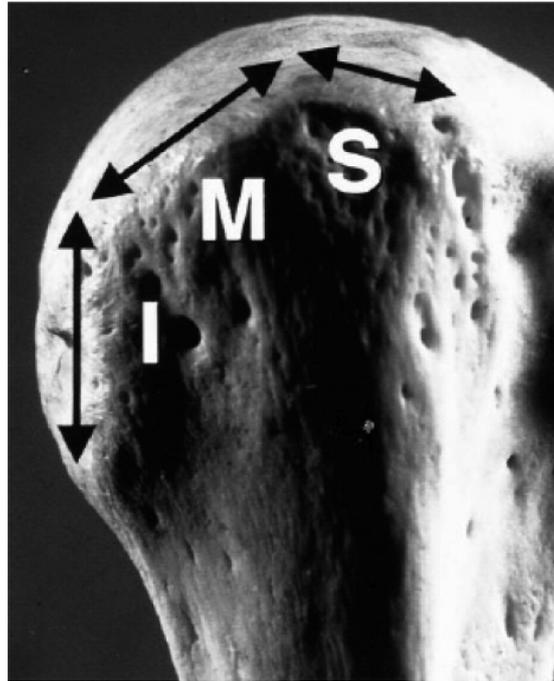


Figure 1-5: Proximal humerus, showing the 3 facets of greater tuberosity (superior [S], middle [M] and inferior [I]). (source: Defranco and Cole<sup>13</sup>)

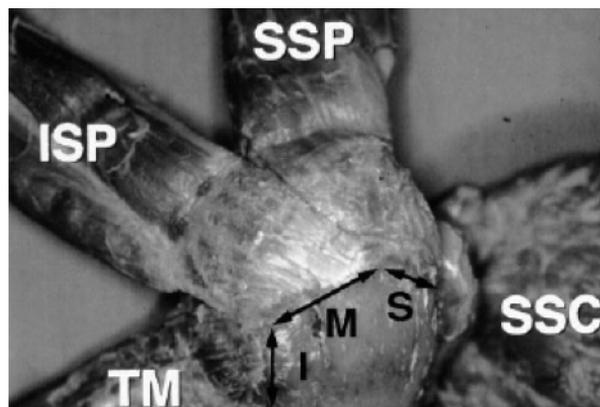


Figure 1-6: Insertion points of rotator cuff tendons<sup>14</sup> (TM: Teres Minor, ISP: Infraspinatus, SSP: Supraspinatus, SSC: Subscapularis, I: Inferior, M: Middle, S: Superior). (source: Minagawa et al<sup>14</sup>)

#### 1.4.2 Function

The upper arm can assume an infinite number of positions at the shoulder joint, which allows the hand and forearm to function effectively. To achieve that, the shoulder joint complex does sacrifice some of its stability as compared to the hip joint for the sake of extra mobility. The major function of the four rotator cuff

muscles is to work in tandem with each other to allow the arm to move relatively freely in numerous positions and at the same time maintain dynamic stability at the glenohumeral joint.

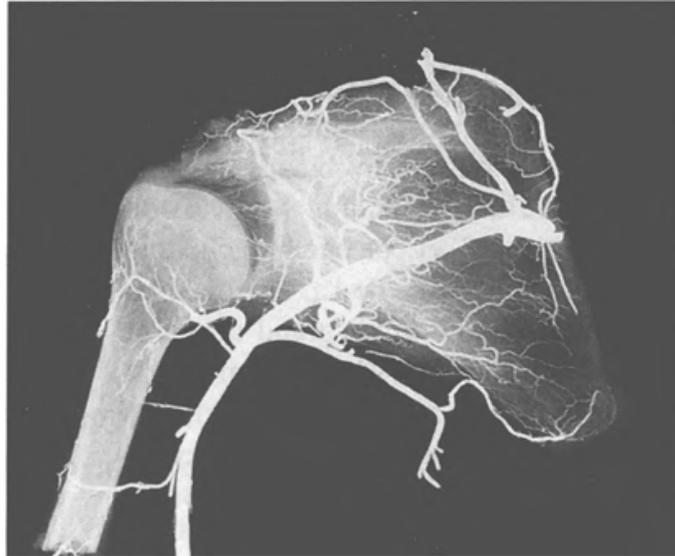
The rotator cuff maintains the humeral head centered on the glenoid and opposes the superior translatory and shearing force of the deltoid by compressing the humeral head in the glenoid concavity. It manages to keep the humeral head constrained within a couple millimeters of the center of the glenoid fossa throughout most of the arc of shoulder motion. The rotator cuff muscles are also tightly adherent to the glenohumeral joint capsule near their insertions onto the humeral tuberosities and reinforce it<sup>16</sup>.

In addition to working synergistically, all these muscles have individual functions as well. The subscapularis is an internal rotator, the supraspinatus works closely with deltoid to produce flexion and abduction, infraspinatus and teres minor are external rotators at the shoulder.

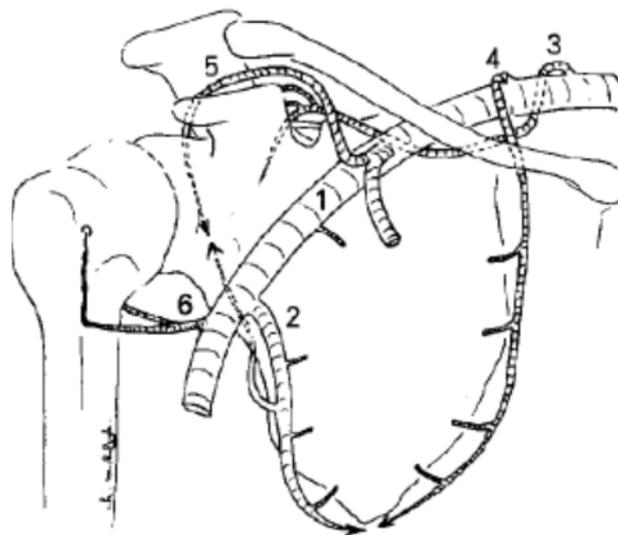
### **1.4.3 Vascularity**

The rotator cuff derives its blood supply from arteries originating from both the muscular and osseous attachments of the cuff<sup>17,18</sup>. The principal blood supply to the rotator cuff comes from branches of the anterior and posterior circumflex humeral arteries (Figure 1-7, Figure 1-8). The anterior humeral circumflex artery and its intraosseous terminal branch, the arcuate artery, along with suprascapular artery supplies the anterior portion of the rotator cuff<sup>17-20</sup>. The posterior humeral circumflex artery perfuses the posterior portion of the rotator

cuff<sup>17,19,20</sup>. Blood vessels from the acromial branch of the thoracoacromial trunk, the subscapular and the suprahumeral arteries may also supply the rotator cuff to varying degrees<sup>17,19,20</sup>.



**Figure 1-7: Anteroposterior X-ray of right shoulder showing pattern of blood supply. (source: Determe et al<sup>19</sup>)**



**Figure 1-8: Blood supply of the rotator cuff, main arteries: 1. Axillary; 2. Subscapular; 3. Suprascapular; 4. Posterior scapular; 5. Acromial branch of the thoracoacromial; 6. Anterior and posterior circumflex humeral. (source: Determe et al<sup>19</sup>)**

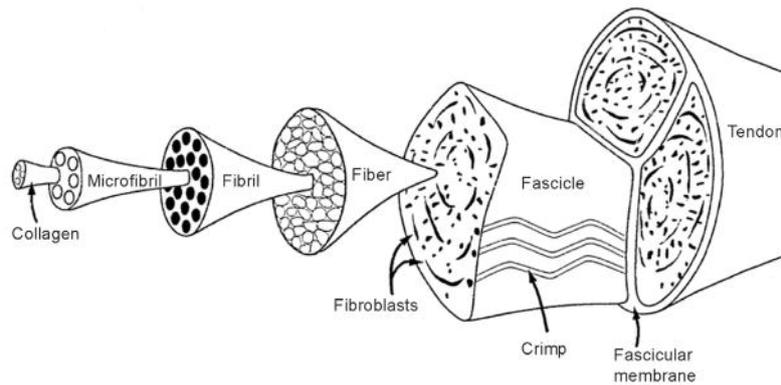
Although there is a broad agreement about the arterial supply of the rotator cuff, several studies suggest that blood supply is not uniform within the

supraspinatus tendon. Conflicting evidence in the literature has led to a debate principally focused on whether there is an area of relative hypovascularity in the supraspinatus tendon<sup>18,19,21-27</sup>. This area, called the “critical zone” by Codman<sup>28</sup> is located 10-15mm proximal to the insertion of the supraspinatus tendon on to the humeral tuberosity and can make it vulnerable for damage. The studies that tend to support the presence of a critical zone are primarily older in-vitro studies<sup>18,19,21-23</sup> while recent in-vivo physiological studies failed to show a hypovascular zone<sup>25-27</sup>.

## **1.5 Tendon structure**

### **1.5.1 General tendon structure**

Healthy tendon is a complex, highly organized material made up of collagen fibrils embedded in a matrix of proteoglycans. The basic structure of a tendon consists of bundles of collagen fibrils, organized in a hierarchical manner<sup>29</sup> (Figure 1-9). Type I collagen molecules join together to form micro fibrils. Adjacent micro fibrils interdigitate and form the next level structure termed a fibril (50-200 nm in diameter). Fibrils then pack into larger structures to form fibers (3-7  $\mu\text{m}$  in diameter). Fibers combine to form fascicles (with diameters on the order of micrometers) and finally, fascicles are bundled together to form the tendon (diameter on the order of millimeters or centimeters)<sup>29</sup>. This type of hierarchical structure aligns fiber bundles with the long axis of the tendon and affords the tendon’s tensile strength.



**Figure 1-9: The hierarchical organisation of tendon (source: Killian et al<sup>29</sup>).**

The extracellular matrix of tendons is composed of: collagen (65 to 80% dry weight), elastin (1 to 2%) and ground substance. Type I collagen is the predominant collagen type and provides the tendons with strength to withstand high loads. Elastin provides flexibility and elastic properties while ground substance consists of approximately 60 to 80% water, proteoglycans and glycoproteins<sup>30</sup>. Tenoblasts and tenocytes make up 90 to 95% of the cellular elements of tendons. They are arranged in parallel rows between the collagen fibers. Tenoblasts are immature spindle-shaped tendon cells with high metabolic activity as shown by their abundant cytoplasmic organelles. As they mature, tenoblasts transform into tenocytes. Chondrocytes, synovial cells and endothelial cells make up the remaining cellular elements of the tendon<sup>31</sup>.

The tendon is enveloped by an epitenon which is a thin, loose connective-tissue sheath containing the vascular, lymphatic and nerve supply to the tendon. It extends within the tendon between the tertiary bundles as the endotenon, investing each tendon fiber. Superficially, the epitenon is surrounded by paratenon, a loose areolar connective tissue consisting of type I and III collagen fibrils, some elastic fibrils, and an inner lining of synovial cells. The space

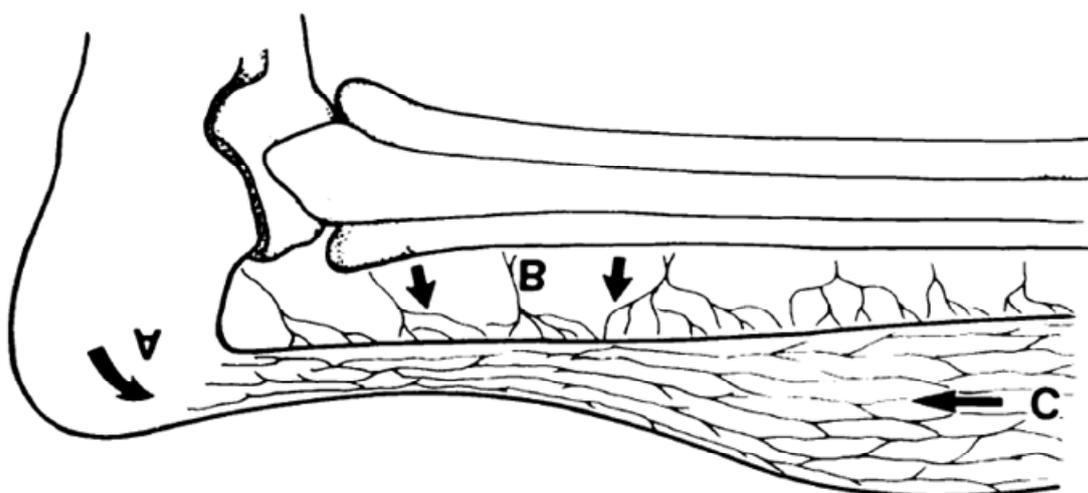
between these two layers contains fluids rich in mucopolysaccharides that provide lubrication, prevent friction and protect the tendon<sup>30</sup>. Tendons present in areas subjected to increased mechanical stress, such as tendons of the hands and feet have synovial tendon sheaths to provide efficient lubrication<sup>31</sup>.

Tendons consume 7.5 times lower oxygen compared with skeletal muscles<sup>32</sup>. This low metabolic rate combined with a well-developed anaerobic energy generation capacity reduces the risk of ischemia and necrosis when carrying loads under tension for long periods. However, a low metabolic rate results in slow healing after injury<sup>31</sup>. Tendons also have differences in their structure, composition, cell phenotypes, and metabolism, based on the functional demands placed on them in specific anatomic locations<sup>33,34</sup>. There is evidence of different rates of collagen turnover, which is higher in stressed tendons such as the supraspinatus but much lower in tendons that are not under high stress<sup>30</sup>.

### **1.5.2 Tendon blood supply**

Tendons are metabolically active tissues and therefore needs a source of blood supply. They receive their blood supply from two main sources<sup>31,35</sup>:

1. Intrinsic supply at the musculotendinous junction (MTJ) and osteotendinous junction (OTJ).
2. Extrinsic supply via the paratenon or the synovial sheath, where present.



**Figure 1-10: Diagram of the blood vessels of the calcaneal tendon showing supply from A- the osteotendinous junction, B- the mesotenon and C- the musculotendinous junction. (source: Carr and Norris<sup>35</sup>)**

The relative contribution of blood supply from each source varies from tendon to tendon. At the MTJ, perimyseal vessels originating from the muscle continue between the fasciculi of the tendon, but they are unlikely to extend beyond the proximal third of the tendon<sup>35</sup> (Figure 1-10). At the OTJ, the blood supply is sparse and restricted to the insertional part of the tendon, although communication may exist between the periosteal vessels and vessels from the extrinsic system at the OTJ<sup>35</sup>.

In tendons with a synovial sheath, blood vessels pass through the vincula (mesotenon) and form a plexus on the surface of the sheath<sup>36</sup>. The superficial part of the tendon is supplied from this plexus while some vessels penetrate the epitenon and run in the endotenon septae to form a connection between the peri-tendinous and intra-tendinous vascular network. In tendons without a synovial sheath, the paratenon provides this extrinsic component by forming a complex vascular network on its surface<sup>31</sup>.

Tendon vascularity can be compromised at junctional zones and at sites of torsion, friction or compression<sup>31</sup>. Angiographic studies have shown a zone of hypovascularity just proximal to tendon insertion in achilles<sup>35</sup>, supraspinatus<sup>18,21</sup> and the flexor digitorum profundus tendons<sup>37</sup>, although laser Doppler flowmetry studies have contradicted those findings<sup>25,38</sup>.

### 1.5.3 Supraspinatus tendon

The structure of supraspinatus tendon has important clinical relevance as they go through a wide range of movement<sup>39</sup>. Asynchronous movements can occur within the tendon structure, where parts of the tendon may become relatively “longer” and the opposite side fibres become “shorter”. For example, when the arm is fully abducted at the shoulder from an adducted position, the articular surface fibres of the supraspinatus become “stretched” (longer) and the bursal-surface fibres “compressed” (shorter). This may contribute to shear stress within the tendon and predispose to pathology<sup>39</sup>.

Fallon et al described four structural subunits within the supraspinatus tendon: tendon proper, attachment fibrocartilage, rotator cable and capsule<sup>40</sup>. The tendon proper is made up of between six and nine structurally independent parallel fascicles covered by endotenons and separated by proteoglycans<sup>12,40</sup>. The proteoglycans in the tendon help to lubricate the fascicles as they moved relative to each other thereby minimizing shear stress<sup>40,41</sup>. The tendon proper inserts into the greater tuberosity through the attachment fibrocartilage. Fibrocartilage is better able to resist compression<sup>42</sup> and supraspinatus tendon is unique in having an extended fibrocartilage. Most epiphyseal tendon

attachments to bone typically have 0.5-0.7mm of fibrocartilage<sup>43</sup> but it is extended to about 20 mm in supraspinatus tendon<sup>40</sup>.

The rotator cable consists of densely packed unidirectional collagen fibres extending from the coracohumeral ligament anteriorly to the infraspinatus posteriorly<sup>44</sup>. It runs perpendicular to the axis of the tendon proper, deep to the tendon and superficial to the joint capsule<sup>40</sup>. The rotator cable is a substantial structure and plays an important role in stress transfer at the tendon insertion<sup>44</sup>.

Clark et al have further described the tendinous insertions of supraspinatus and infraspinatus as a five-layer structure<sup>12</sup> (Table 1-2, Figure 1-11). Layer two forms the main portion of the tendon. Layer four corresponds to the rotator cable described by Burkhart<sup>44</sup> and Fallon<sup>40</sup>, which functions like a load bearing suspension bridge distributing load and stress shielding the distal tendon<sup>44</sup>.

Layer	Thickness	Composition
1	1 mm	Superficial fibres of the coracohumeral ligament.
2	3 – 5mm	Closely packed parallel tendon fibres grouped in large bundles. Extend directly from muscle belly to humerus.
3	3 mm	Tendinous structure with smaller fascicles and less uniform orientation than in layer 2
4	Variable	Deep fibres of coracohumeral ligament along with loose connective tissue containing thick bands of collagen that run perpendicular to layer 2
5	1 – 2 mm	Capsular layer made of a continuous sheet of interwoven collagen fibrils

**Table 1-2: Histological layers of the supraspinatus and infraspinatus tendons as per Clark et al. (source: Clark and Harryman<sup>12</sup>).**

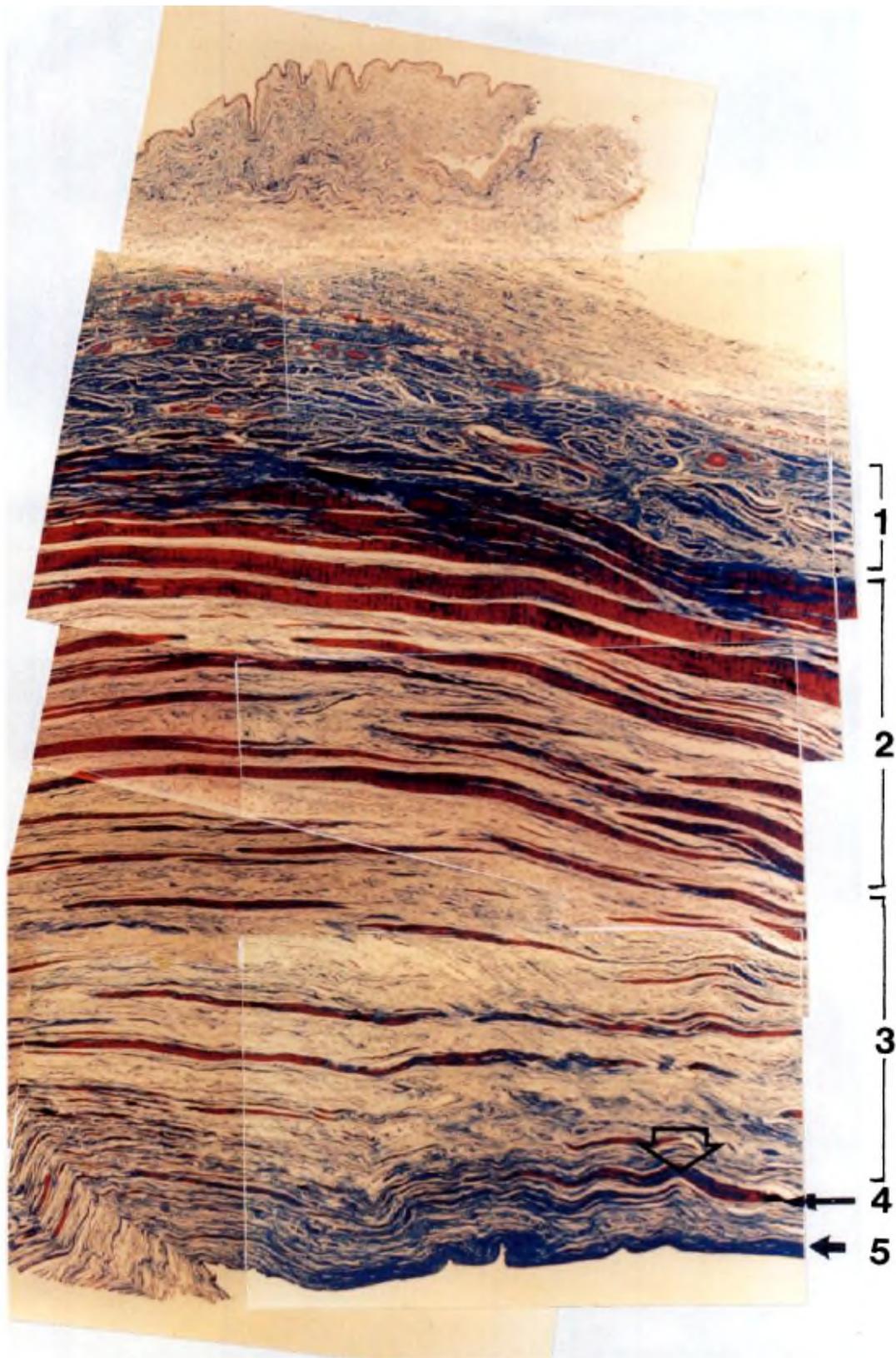


Figure 1-11: Composite photomicrograph of a vertical, longitudinal section through the supraspinatus tendon and joint capsule near the insertion of the tendon. Numbers 1-5 represent the layers (source: Clark and Harryman<sup>12</sup>).

## 1.6 Conclusion

In summary, the supraspinatus is a specialized tendon capable of internal compensation through structurally independent fascicles, which can slide past one another. The tendon attachment is adapted to resist compression and disperse tensional load.

In the following chapter I will discuss the pathology of rotator cuff disorders and provide an overview on the modalities available to diagnose and treat these disorders.

## Chapter 2 Pathology, diagnosis and treatment of rotator cuff disorders

### Summary:

*In this chapter, I will discuss the different theories proposed for rotator cuff pathology and outline the current methods of diagnosis, with particular emphasis on ultrasound and the current range of treatment options. From this, the basis for this thesis with respect to my study of the shoulder will be demonstrated.*

### Declarations:

*None*

## 2.1 Pathology

Rotator cuff tendons, supraspinatus in particular can be affected by pathology such as tendinopathy, bursitis, and impingement syndrome to tears of one or more tendons. Cadaveric studies have shown an incidence of cuff tear ranging from 5% to 30%<sup>46</sup>, while bursitis, impingement syndrome, and rotator cuff tendinopathy occur in approximately 2% to 18% of the adult population<sup>47</sup>.

Prevalence of rotator cuff tears increases with age. Tempelhof et al conducted a prospective clinical and radiological evaluation of asymptomatic shoulders in volunteers from different age groups and found evidence of a rotator cuff tear in 23% of them<sup>48</sup>. There was a wide variation among the different age groups – the prevalence was only 13% in those aged between 50-59 years going up to 51% in those aged 80 years and above<sup>48</sup>.

### 2.1.1 Definition

Several terms are used in the literature to describe tendon disorders, often interchangeably leading to confusion<sup>49</sup>. The common terms are tendinitis (implying inflammation), tendinosis (a degenerative tendon condition without accompanying inflammation) and tendinopathy (no implication for pathology)<sup>50</sup>.

A uniform terminology to describe tendon disorders is desirable to perform proper research, assessment and treatment<sup>51</sup>.

In the past, the term tendinitis was used to describe any pain arising from an abnormal tendon, thus implying inflammation as the central pathological process. However, various treatment modalities aimed at reducing inflammation around the tendon have reported limited success<sup>52</sup> and histological studies of

surgical specimens consistently show the presence of degenerative lesions, with either absent or minimal inflammation<sup>53,54</sup>. Therefore, the definition of 'tendinitis' has been largely abandoned and the terms 'tendinosis' or, more generically, 'tendinopathy' are now currently preferred<sup>30,49</sup>.

Tendinopathy is a generic term without aetiological, biochemical or histological implications and is used to describe pathology in, and pain arising from, a tendon<sup>39</sup>. Therefore, in the clinical setting it may be appropriate to use the term tendinopathy as it makes no assumption as to the underlying pathologic process<sup>50</sup>. Rotator cuff tendinopathy can lead to progressive failure of the rotator cuff, typically progressing from partial to a full thickness tear of the supraspinatus tendon then extending into the infraspinatus tendon or the subscapularis tendon, or both<sup>55</sup>. The terms tendinopathy, partial thickness tear and full thickness tear are therefore used to describe the full spectrum of rotator cuff disorders.

### 2.1.2 Aetiology

The underlying causes for rotator cuff pathology are poorly understood. The mechanisms responsible for rotator cuff pathology are classically described as extrinsic, intrinsic or a combination of both<sup>56</sup>. Extrinsic factors are defined as those causing compression of the rotator cuff tendons, while intrinsic mechanisms are those associated with degeneration of the tendon. It is still a matter of debate as to whether an intrinsic degenerative change in the tendons or extrinsic mechanical compression is responsible for rotator cuff tears<sup>39,50,57</sup>.

As early as 1931, Codman first described degenerative changes of the tendons that can cause rotator cuff tears<sup>58</sup>. Biopsies of ruptured tendons suggest that full-thickness tears typically result from a chronic degenerative process rather than acute injury<sup>59,60</sup>. In 1949, Armstrong on the other hand suggested that compression of the bursa and rotator cuff tendons under the acromion causes the supraspinatus syndrome<sup>61</sup>. Subsequently, Neer stated that 95% of rotator cuff tears were caused by mechanical impingement secondary to attrition of the cuff with the under surface of the acromion and the coracoacromial ligament<sup>9</sup> and reported successful treatment by anterior acromioplasty<sup>55</sup>.

Various studies have proposed that the aetiology of rotator cuff pathology is multifactorial and attributed pathologic processes both intrinsic and extrinsic to the cuff tendons as the underlying cause<sup>62-67</sup>. Differentiating between intrinsic and extrinsic causes is difficult because very little data exist describing early tendinopathy. Most histologic studies are based on specimens taken at the time of surgery, typically from tendons in the end stages of disease. Recently genetic factors have also been implicated in the pathogenesis of rotator cuff tears<sup>20,50</sup>. However, the precise aetiology is not known.

### **2.1.3 Extrinsic theory**

Extrinsic factors are those that encroach and narrow the subacromial space causing compression of the rotator cuff tendons. These may be anatomical factors like the shape and orientation of the acromion, biomechanical factors like alterations in scapular or humeral kinematics, postural abnormalities, tensile load, training errors or a combination of these<sup>20,56</sup>. Based on his extensive

experience Neer believed that almost all of the tears of the rotator cuff are initiated by impingement wear rather than circulatory impairment or trauma<sup>9</sup>.

### **2.1.3.1 Subacromial impingement**

The subacromial space is the interval between the humeral head inferiorly and the anterior acromion with the coracoacromial arch superiorly. It is generally measured linearly between the acromion and the humeral head and expressed as the acromiohumeral distance (AHD). AHD has been measured in normal shoulders and in patients with rotator cuff disease using plain radiographs<sup>68-71</sup>, ultrasound<sup>72-74</sup> and MRI<sup>70,75,76</sup>.

Several studies have shown that AHD varies from 7–14 mm in healthy shoulders but is reduced in those with rotator cuff tears<sup>71,72,77</sup>. It has also been shown that in patients having surgery for rotator cuff disease, an AHD of less than 7 mm (with the arm at rest) is a predictor for poor outcome<sup>71,77,78</sup>. However, significant subacromial space narrowing with the arm at rest is not always seen in patients with rotator cuff disease<sup>72,74</sup>. Biomechanical factors such as muscle activity and posture may cause a reduction in the subacromial space when the arm is being used. This “functional” narrowing of the subacromial space may only be detected by measuring the space with muscle activation and this measure may prove to be much more useful<sup>75</sup>. Several studies have shown that AHD during active arm elevation was smaller in subjects with rotator cuff disease compared to healthy shoulders<sup>75,76,79</sup>.

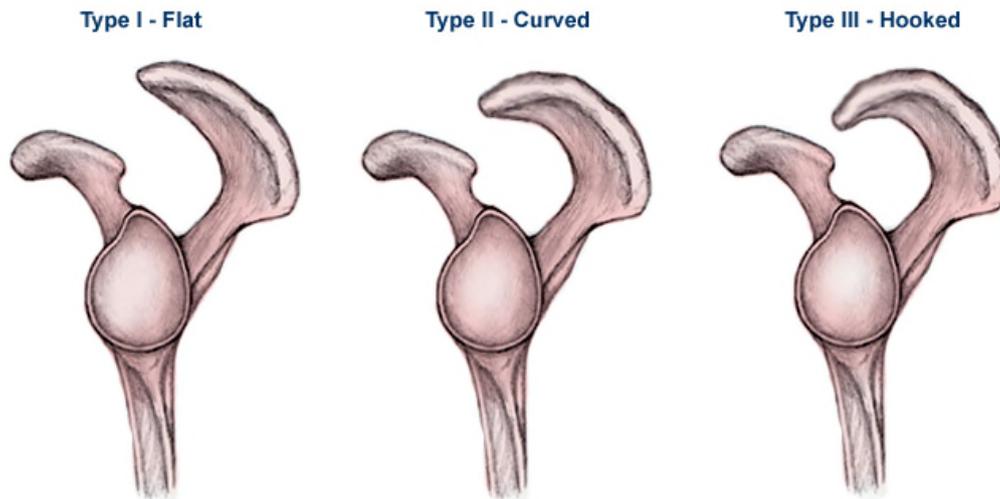
Anatomical factors like variations in the shape, slope or orientation of the acromion and prominent osteophytic changes to the inferior aspect of the acromioclavicular joint (ACJ) or coracoacromial ligament can also reduce the subacromial space excessively and cause impingement<sup>62,63,80-82</sup>.

### **2.1.3.2 Acromion morphology**

The shape of acromion in both coronal and sagittal plane can have a big influence in causing subacromial impingement<sup>9</sup>. Neer believed that anatomic variation and abnormality in the shape of the acromion are the major etiologic factors in rotator cuff tears<sup>9</sup>. Various parameters like acromial type<sup>83</sup>, acromial slope<sup>83,84</sup>, acromial tilt<sup>84</sup>, lateral acromial angle<sup>85</sup> and acromion index<sup>86</sup> have been used to describe acromial morphology. The classification system proposed by Bigliani and co-workers' based on outlet views is widely accepted for the evaluation of acromial morphology in patients with rotator cuff disease<sup>83</sup>. He described three different acromial shapes in relation to full thickness rotator cuff tears (Figure 2-1):

1. Type I acromion has a flat under surface
2. Type II has a curved under surface
3. 3. Type III has an anterior hook (hooked acromion)

A fourth type of acromion was added later that had a convex undersurface<sup>82</sup>.



**Figure 2-1: Bigliani classification of acromial morphology (source: Bigliani et al<sup>83</sup>)**

Bigliani et al found a type III acromion in 70% of cadavers with rotator cuff tears while only 3% of type I acromion was associated with a tear<sup>83</sup>. This observation was supported by Epstein and co-workers, when they found a significant correlation between Type III (hooked) acromion and the presence of rotator cuff tears (62% vs 13%,  $p < 0.0001$ ) using MRI<sup>81</sup>. Others have found that a low lateral acromial angle and a large lateral extension of the acromion are associated with a higher prevalence of impingement and rotator cuff tears<sup>57,80,87,88</sup>.

It is unclear whether the acromial morphology is a congenital or an acquired trait<sup>64,89</sup>. Anatomic studies on cadavers and MRI studies on young symptomless population did not find a single hooked acromion under the age of 30 years<sup>80,90</sup>. With advancing age, a consistent and gradual transition from a flat acromion to a more curved or hooked acromion is seen<sup>64,89,91</sup>. The shape of the acromion can be modified by bone apposition predominantly at the anterior inferior aspect of the acromion. This age-related spur formation may be one of the most important factors in progression to a rotator cuff rupture<sup>92</sup>.

There are arguments against this theory; the main criticisms are:

1. Most partial thickness cuff tears do not occur on the bursal surface of the cuff where mechanical abrasion from acromion is expected to occur<sup>93,94</sup>.
2. A 3D shape analysis of acromial morphology on MRI has shown that osseous impingement by the acromion is not a primary cause of shoulder impingement or rotator cuff tears<sup>95</sup>.
3. There is evidence to suggest that bursal surface cuff tears could be responsible for subacromial spurs and not the other way round<sup>94,96,97</sup>.
4. Although bursal surface partial tears or full thickness tears are associated with severe degenerative changes in the acromion, studies have shown that these changes can be present when the rotator cuff is normal<sup>98</sup>.
5. There is poor intra and inter observer reliability in identifying the acromion type in both anatomic and radiological assessment<sup>99-101</sup>.
6. Recent studies have shown that routine acromioplasty may not be necessary for successful rotator cuff repair<sup>102</sup>, which would be unexpected if acromial shape plays a major role in causing tendon damage.

To summarise, most evidence suggests that subacromial impingement remains a valid theory. It may play a major role in selected cases of rotator cuff disease but is probably not as common as previously thought.

#### **2.1.3.3 Biomechanical factors**

Postural abnormalities, focal muscle weakness or soft tissue tightness can have a direct influence on scapular and humeral kinematics. Abnormal scapular and

humeral kinematics can lead to dynamic narrowing of the subacromial space causing compression of the rotator cuff tendon secondary to superior translation of the humeral head<sup>103-106</sup>.

Reduced posterior tilting and upward rotation of the scapula but an increase in internal rotation were found in patients with subacromial impingement compared to normal subjects<sup>107-109</sup>. This can result in the failure of the anterior acromion to move away from the humeral head during arm elevation and can contribute to a reduction in the subacromial space and compression of the rotator cuff tendons<sup>109</sup>. Many authors have identified anterior acromion as the predominant site for impingement<sup>9,55,110,111</sup>. Thoracic spine kyphosis and even small changes in the performance of scapulothoracic muscles particularly the serratus anterior and trapezius can alter the position of the scapula and contribute to a reduction in the subacromial space<sup>56,112,113</sup>.

#### **2.1.3.4 Internal impingement**

The term “internal impingement” refers to compression of the rotator cuff tendons between the posterior superior glenoid rim and humerus when the arm is in full external rotation, abduction, and extension<sup>114,115</sup>. This happens on the articular surface rather than the bursal surface of the tendons and is particularly found in overhead athletes<sup>114,116-118</sup>. Although described as an extrinsic mechanism, narrowing of the subacromial space is not a typical finding. Patients tend to present with pain in the posterior and superior aspects of the shoulder typically in the late cocking phase of throwing when the arm is in abduction and external rotation<sup>116</sup>

#### **2.1.3.5 Tensile load**

The exact level of load to maintain ideal tendon homeostasis is unknown. With overuse, several studies have demonstrated pathological changes in tendon such as tenocyte apoptosis, chondroid metaplasia and changes in matrix metalloproteinases<sup>52,119,120</sup>. Others believe that under stimulation may be as damaging as over stimulation<sup>66</sup>. It may explain why degeneration happens in certain ageing population and not in others<sup>50,65</sup>. The increased incidence of tendinopathy with age and in the active population is consistent with this theory. This theory does not fully explain why certain areas of particular tendons are particularly prone to degenerative change.

#### **2.1.4 Intrinsic theory**

A growing body of evidence suggests that intrinsic factors may cause degeneration of the tendon and initiate the rotator cuff changes<sup>58,97,121,122</sup>. Specifically, factors such as age, microvascularity, altered biology and inferior mechanical properties have been proposed. Genetics and environmental factors like smoking may also play a part.

##### **2.1.4.1 Age**

Advancing age in itself can have a negative effect on mechanical properties of tendons, due to reduced arterial blood flow, local hypoxia, free radical production, impaired metabolism and nutrition<sup>123</sup>. This may explain the increased prevalence of rotator cuff degeneration, including partial and full thickness rotator cuff tears in subjects over 40 years<sup>48,124-126</sup>. Although Neer advocated an extrinsic mechanism for rotator cuff pathology, he included age as an important factor. He described rotator cuff pathology as a continuum with 3

stages characterized by age: less than 25 years for stage I, between 25 and 40 years for stage II, and greater than 40 years of age for stage III respectively<sup>9</sup>.

Histological studies have shown that, with advancing age supraspinatus tendons have decreased glycosaminoglycans and proteoglycans<sup>127</sup>. Kumagai et al found calcification and fibro vascular proliferation, with an overall reduction of collagen content and an increased proportion of weaker, more irregularly arranged type III collagen in the rotator cuff tendons of elderly subjects without history of shoulder problems<sup>128</sup>.

On the contrary, Longo et al in a study on elderly population found little evidence to support the theory that tendon degenerates with age in healthy asymptomatic individuals<sup>129</sup>. Along with Matthews et al<sup>67</sup>, he suggests that there are other factors beyond age that causes degeneration and that separate pathways exist in the ageing symptomatic and asymptomatic rotator cuff<sup>129</sup>. Regardless, age related changes to the tendon appear to be a significant intrinsic factor in the pathogenesis of tendinopathy.

#### **2.1.4.2 Microvascularity**

Tendons are metabolically active structures and require vascular supply for nutrition and turnover. Reduced vascularity may reduce collagen synthesis and compromise tendon turnover. Certain tendons are susceptible to vascular compromise; these include the supraspinatus<sup>21-23</sup> and the achilles<sup>38,130</sup>. A deficient vascular supply has been implicated as a factor in the pathogenesis of human rotator cuff tendinopathy.

Codman first described the idea of a “critical zone” as an area within the supraspinatus tendon with decreased vascularity and the most common site for tendon pathology<sup>28</sup>. He described this area to be approximately 1 cm medial to the insertion of the supraspinatus on the greater tuberosity. Subsequent studies about the blood supply within the supraspinatus tendon concluded that the blood supply may not be uniform and concur with the presence of a “critical zone”, which can make the tendon more susceptible to damage at that particular region<sup>21-23</sup>. It has also been suggested that this “critical zone” with its sparse blood supply may not be a well-defined anatomical zone but could be a functional zone dependent on arm position<sup>23</sup>. This concept of a reduced blood flow has been challenged by in-vivo studies which did not find any evidence of hypo-vascularity in the “critical zone”<sup>25-27</sup>.

Blood supply can also be reduced with increasing age<sup>18,22,131,132</sup> and at the articular side fibres compared to the bursal surface fibres, which appear to be well vascularised<sup>21,131</sup>. Neovascularization or an increased vascular response has been found in regions of degenerative changes and smaller tendon tears<sup>25,122,133,134</sup> while tendinopathy that progress to complete tendon tears have been shown to be avascular<sup>67,133,135</sup>. It has been suggested that the increased vascularity could be a healing response to tissue microtrauma while the avascularity could be the cause of progressive tendinopathy or the result of a complete tear<sup>23,25</sup>.

Still, the relationship between vascularity, age and degeneration has not been fully elucidated and a recent review article has highlighted the lack of definitive

knowledge in this field<sup>20</sup>. Besides, the vascular and impingement theories are not mutually exclusive. The high incidence of supraspinatus pathology can be explained as the result of impingement in and around a critical zone of vascular supply<sup>136</sup>.

#### **2.1.4.3 Genetics**

In a study by Harvie et al<sup>137</sup>, siblings of patients with full thickness rotator cuff tears were found to be at a significant risk of experiencing both symptoms of rotator cuff disease and tears of the rotator cuff. The study showed that siblings had more than twice the risk of developing tears of the rotator cuff (relative to a control group) ( $p < 0.001$ ) and nearly five times the risk of experiencing symptoms ( $p < 0.001$ ). A case-control study by Flynn et al<sup>138</sup> reported that individuals with an ACL tear are twice as likely to have a relative with an ACL tear and more than twice as likely to have a first-degree relative with an ACL tear. Several studies have reported a relationship between genetics and Achilles tendinopathy<sup>139-141</sup>.

Taken together these results appear to hint at a genetic predisposition to rotator cuff tears. However, the identification of several intrinsic and extrinsic risk factors associated with rotator cuff tears, suggests that complex gene–environment interactions are probably involved in the aetiology of these conditions.

#### **2.1.5 Other factors**

Increased levels of substance P, a neurotransmitter, has been found in rotator cuff tendinopathy<sup>142</sup>. Other studies have shown increased levels of

neuropeptides and neurotransmitters such as acetylcholine<sup>143,144</sup>, catecholamines<sup>145,146</sup>, glutamate<sup>147</sup> and mast cells<sup>148</sup> in tendon disorders suggesting a possible neural aetiology.

Epidemiological studies have helped to identify several other risk factors for rotator cuff disease. An increased level of total cholesterol, triglycerides and LDL with reduced HDL is related to full thickness tears<sup>149</sup>; suggesting diet may play a part in tendon homeostasis. Tobacco has been shown to increase the risk for rotator cuff tear<sup>150</sup>, tear size<sup>151</sup> and poorer outcome after repair<sup>152,153</sup>. Heavy manual work and exposure to vibration are shown to be risk indicators for tendinitis of the shoulder<sup>154</sup>. Systemic diseases, either inherited (such as Marfan's or Ehlers-Danlos syndrome) or acquired (such as Rheumatoid arthritis or Diabetes Mellitus) may also influence tendon pathology<sup>155-157</sup>.

#### **2.1.6 Conclusion**

In practice, it is likely that rotator cuff disease arises from a combination of all the above factors, rather than being a process that is purely intrinsic or extrinsic to the tendons itself, although their relative contributions may vary and difficult to assess. Damage accumulation from repetitive microtrauma and aging are likely to contribute to the process<sup>158</sup>. Despite the high prevalence of rotator cuff disease, the inciting element for tendinopathy and tears is not known. A major limitation is borne by the fact that examination of human tendons is only possible in patients with advanced disease who undergo surgery while tissues from patients in the early phase of disease or who are treated conservatively are not available for study.

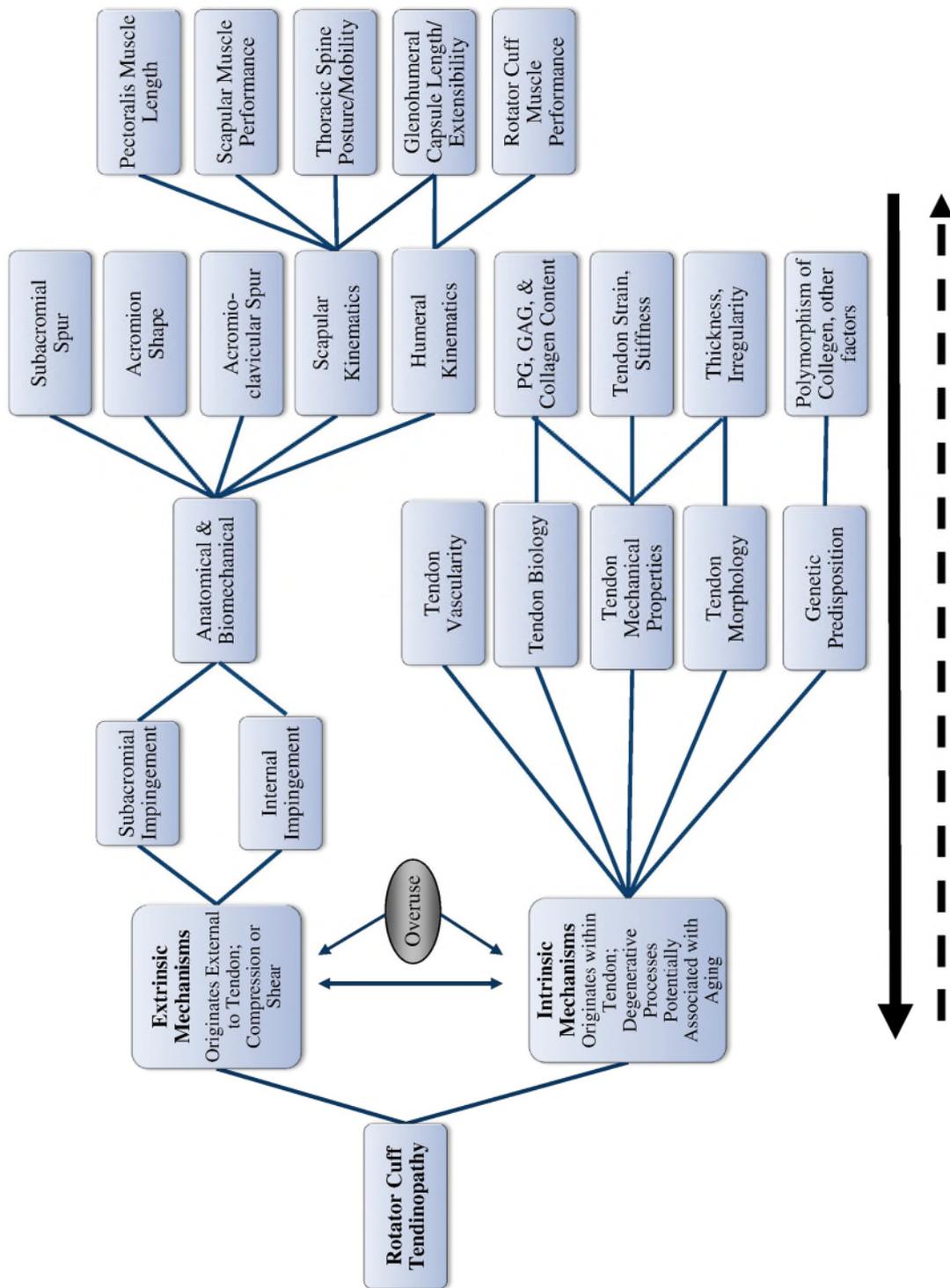


Figure 2-2: Extrinsic and intrinsic mechanisms of rotator cuff tendinopathy (from: Seitz et al<sup>56</sup>)

## 2.2 Diagnosis of rotator cuff pathology

Traditionally, clinicians have relied on a clinical examination comprising a detailed subjective history and comprehensive physical examination, followed by specific clinical tests to diagnose pathology in the rotator cuff.

### 2.2.1 Clinical presentation

#### 2.2.1.1 Symptoms and signs

The physical signs and symptoms of disease of the rotator cuff are often non-specific<sup>159</sup>. Pain, weakness, and loss of shoulder motion are common symptoms reported with rotator cuff pathology<sup>160</sup>. The symptoms and signs can broadly be categorized under two categories<sup>159</sup>:

1. Those caused mainly by the inflammation of subacromial bursa and tendon – shoulder pain, a painful arc, positive impingement sign and signs of fluid in the bursa.
2. Those resulting from a torn tendon – crepitus, muscle weakness, drop arm sign and atrophy of the spinati.

Pain is the most common symptom and is usually felt over the anterolateral part of the shoulder. It is often referred to the level of the deltoid insertion and is exacerbated by overhead activities. Night pain is a frequent symptom, especially when the patient lies on the affected shoulder<sup>159</sup>. Patients may also report clicking, catching or crepitus in the shoulder<sup>160,161</sup>. Symptoms may be relatively acute, either following an injury or associated with a known repetitive overuse activity. In elderly patients with degenerative cuff pathology, symptoms are often insidious with progressive pain, weakness and loss of active motion<sup>160,162</sup>.

However, many degenerative rotator cuff defects are asymptomatic<sup>163,164</sup>.

### 2.2.1.2 Examination

Physical examination is an important part of the clinical assessment of patients presenting with shoulder pain and weakness. Inspection may reveal supraspinatus and infraspinatus atrophy in massive rotator cuff tears<sup>160</sup>. Palpation at the anterior edge of the acromion may reveal an area of tenderness or defect in the cuff-tendon attachment<sup>160</sup>. The impingement syndrome associated with rotator cuff injuries tends to cause pain with elevation ranging from 60-120° when the rotator cuff tendons are compressed against the anterior acromion and coracoacromial ligament<sup>9,165</sup>. Decreased active elevation with normal passive range of motion may be observed in rotator cuff tears due to pain and weakness. Individual muscles can be isolated and tested for strength<sup>166</sup>. In patients with massive cuff tears, the humeral head is no longer stabilized in the glenoid and the deltoid muscle is ineffective in elevating of the arm, leading to a finding known as pseudo paralysis of the shoulder<sup>167</sup>.

Numerous tests have been described to evaluate the presence of impingement syndrome and to determine the integrity of the individual components of the rotator cuff<sup>168</sup>. Many similar tests have been described by different people but given different names. Also, the same person may have described many different tests, which can lead to confusion. Neer described an impingement test and an impingement sign<sup>9,55</sup>. The “impingement sign” was an injection test, where the pain elicited by the “impingement test” was relieved by the injection of 10 ml of 1% lignocaine beneath the anterior acromion<sup>9</sup>. He stated that this test could separate impingement lesions from other causes of shoulder

pain. Other tests include the Hawkins-Kennedy impingement sign<sup>165</sup>, Jobe's empty can test<sup>166</sup>, the horn-blower's sign<sup>169</sup>, the drop-arm sign described by Codman<sup>28</sup>, Gerber's lift off<sup>170</sup> and the belly press test<sup>171</sup> and the infraspinatus muscle strength test<sup>172</sup>, to name a few.

Several studies have commented that most tests for rotator cuff pathology were inaccurate and therefore cannot be relied upon for making an accurate diagnosis<sup>173-177</sup>. The poor accuracy of clinical tests for rotator cuff pathology could be related to a lack of anatomical validity of the tests or it may be that the close relationships of structures in the shoulder may make it difficult to identify specific pathologies with clinical tests<sup>174</sup>

### **2.2.2 Investigations**

Accurate diagnosis of shoulder conditions by clinical examination alone is difficult as the clinical findings are often shown to have poor correlation with the actual pathology<sup>175-178</sup>. It has been suggested that the close relationship of the structures in the shoulder may explain the poor diagnostic accuracy of clinical tests for rotator cuff pathology<sup>179</sup>. Imaging, therefore is important in the management of patients with shoulder pain, particularly for the surgeon who require detailed information to advice patients about their treatment options, prognosis and outcome especially where surgery is considered. In particular, it is important for the surgeon to know about the presence or absence of a rotator cuff tear and its extent, so that the appropriate surgery could be planned. Many studies have demonstrated that the size of the tear has a strong correlation to the likelihood of a satisfactory final outcome<sup>180-182</sup>. But, even a global clinical

assessment of shoulder function is relatively poor in predicting the size of rotator cuff tear<sup>183</sup>.

The clinician has a choice among the many available imaging techniques for the evaluation of rotator cuff tendons in the shoulder. These include ultrasonography, MRI and arthrography (Conventional, CT or MR). Plain radiographs of the shoulder may be useful to exclude osteoarthritis of the glenohumeral or acromioclavicular joints and calcific tendonitis. Conventional and CT arthrography use ionising radiation and have largely been replaced by Ultrasonography (USG), Magnetic Resonance Imaging (MRI) and Magnetic Resonance Arthrography (MRA).

Currently, Ultrasonography, Magnetic Resonance Imaging and Magnetic Resonance Arthrography are the three main imaging modalities used in the assessment of rotator cuff pathology<sup>162,184</sup>. A meta-analysis comparing the diagnostic accuracy of MRA, MRI and USG has shown that MR Arthrography is more sensitive and specific than either MRI or ultrasound in diagnosing full-thickness or partial-thickness rotator cuff tears, when referenced against surgical findings<sup>184</sup>. The same study also showed no significant differences in either sensitivity or specificity between MRI and ultrasound in the diagnosis of partial- or full-thickness rotator cuff tears<sup>184</sup>.

#### **2.2.2.1 *Ultrasound***

Since Seltzer's first description in 1979<sup>185</sup>, USG of the shoulder is used in secondary and, increasingly, primary healthcare settings to evaluate the integrity

of the rotator cuff. USG is a non-invasive examination that allows dynamic visualisation of the tendons during movement of the shoulder and has practically no adverse effects. It is quick, portable, cost-effective and more acceptable to the patient compared to arthrography<sup>184,186</sup>. However, USG has a long learning curve and its accuracy very much depends on the skill of the operator. Its effectiveness is also somewhat limited in obese patients, patients with a reduced range of motion and especially in the diagnosis of partial thickness tears<sup>162,184,187</sup>.

#### **2.2.2.2 Magnetic Resonance Imaging**

Magnetic Resonance Imaging has become the primary diagnostic method for the evaluation of joints by virtue of its non-invasive nature, lack of ionizing radiation, superior soft tissue contrast and ability to outline structures in multiple planes<sup>188</sup>. Direct magnetic resonance arthrography (MRA) extends the capabilities of conventional MR imaging<sup>189</sup>. MRA is a two-step procedure involving intra-articular instillation of contrast solution followed by MR imaging. Diluted gadolinium is usually injected as the MR arthrographic contrast material<sup>189</sup>. The arthrogram can be performed using fluoroscopy or in the case of shoulder, by USG. Arthrography is an invasive procedure with its associated risks<sup>190</sup> and MRI is time consuming and costly.

When rotator cuff pathology is suspected, the decision to perform appropriate imaging is usually based on patient's age and diagnostic questions that need to be addressed. Conventional MRI and USG have high sensitivity (92-94%) and specificity (92-94%) for full-thickness tears, comparable to MRA<sup>162,184</sup>.

Therefore, it may be sufficient in older patients in whom surgery might be

considered to repair a full thickness rotator cuff tear. For partial-thickness tears, USG and MRI have much lower reported sensitivities of only 52–74%<sup>162,184</sup>. In addition, inter- and intra-observer agreements are substantially decreased in partial-thickness compared to full-thickness tears of the rotator cuff<sup>191-194</sup>. A lack of knowledge about the normal thickness of rotator cuff tendons may be a factor as one of the criteria often used to diagnose a partial-thickness rotator cuff tear is thinning of the tendon<sup>195-197</sup>. MRA is therefore the most sensitive modality at present for diagnosing partial thickness rotator cuff tears with a statistically significant difference compared to USG and MRI<sup>184</sup>.

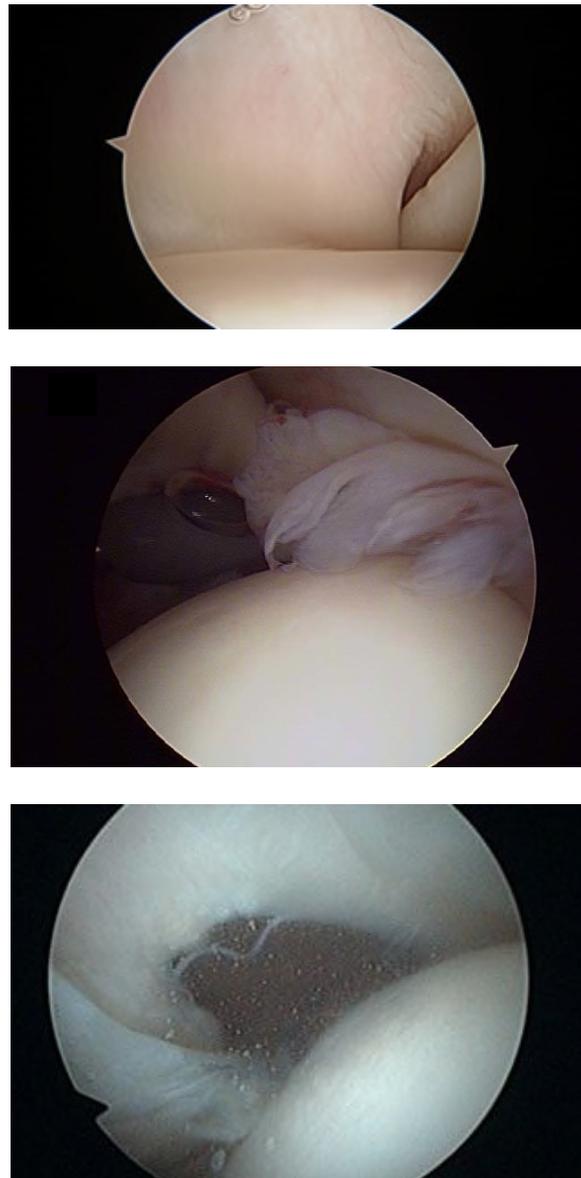
## **2.3 Treatment**

The objectives of treatment of symptomatic rotator cuff disease are to relieve pain and restore movement and function of the shoulder. A wide spectrum of treatment options are available to treat rotator cuff disease. These vary from conservative methods like rest, physical therapy, oral medications and subacromial injections to surgical options like arthroscopic or open subacromial decompression, acromioplasty and repair of the rotator cuff tendons<sup>47,55,198-201</sup>

### **2.3.1 Natural history**

The pathophysiology of rotator cuff disease has traditionally been viewed as a progressive disorder of the rotator cuff tendons that begins with an acute tendinitis, progressing to tendinosis with degeneration and partial thickness tears and finally resulting in full-thickness rotator cuff tears<sup>9,56</sup>. Yamaguchi et al performed a longitudinal analysis of asymptomatic tears as a model to evaluate the natural history of rotator cuff tears<sup>202,203</sup>. They found that a substantial

proportion of subjects with asymptomatic rotator cuff tears become symptomatic after a short-term follow-up period with an increase in pain and decrease in ability to perform activities of daily living. USG examination showed that 50% of the symptomatic patients and 22% of the asymptomatic patients showed tear progression<sup>202</sup> with an increase in tear size of full-thickness tears and the progression of partial tears to full-thickness tears<sup>203</sup>.



**Figure 2-3: From top to bottom – arthroscopic images of normal, articular sided partial thickness tear and full thickness tear of the rotator cuff**

Milgrom et al studied the integrity of the rotator cuff in both dominant and non-dominant shoulders of 90 asymptomatic adults between the ages of 30 and 99 years using ultrasound<sup>124</sup>. They noticed that the prevalence of partial- or full-thickness tears increased markedly after 50 years of age. Rotator cuff tears were present in over 50% of dominant shoulders in the seventh decade and in 80% of subjects over 80 years of age. While most lesions in the fourth and fifth decades were either stage 1 or 2, all stage 3 lesions in that age group were only partial thickness tears. In contrast, 55% of lesions in the sixth to tenth decades were full thickness tears, suggesting that at least some of the stage 1 or 2 lesions progress on to full thickness tears even in the asymptomatic individuals<sup>124</sup>.

Fukuda et al studied large histologic sections of surgical tissue from 12 patients treated surgically for bursal-side rotator cuff tears (BSRCT)<sup>133</sup>. They observed that superficial BSRCTs develop into deep tears and eventually become full thickness tears. In a study by Maman et al<sup>204</sup> on symptomatic patients, serial MRI studies were done on 59 shoulders with either full or partial rotator cuff tears treated nonsurgically. They found that more than half (52%; seventeen) of the thirty-three full-thickness tears increased in size at follow-up. Therefore, it seems likely that rotator cuff pathology if left untreated can progress along the spectrum of tendinopathy, partial thickness tear to full thickness tear.

### **2.3.2 Non-operative treatment**

Conservative management is often the primary treatment of choice. The mainstays of conservative treatment are physical therapy and oral non-steroidal

anti-inflammatory drugs (NSAIDs) along with subacromial corticosteroid injections.

### **2.3.2.1 Physiotherapy**

Physiotherapy is a broad term and can include range of motion, stretching, flexibility and strengthening exercises, along with manual therapy and other modalities like ultrasound<sup>205</sup>. Multiple systematic reviews of interventions for rotator cuff pathology and shoulder pain suggest that exercise may be an effective treatment<sup>47,205-207</sup>. Studies have shown that home and supervised exercise programmes might be more effective than no intervention or placebo<sup>200</sup> and that therapeutic exercises have a positive effect on pain and function<sup>205,208</sup>.

In a prospective randomized study Haahr et al have shown that exercises are as efficient as subacromial decompression in patients with subacromial impingement at 4-8 years follow-up<sup>209</sup>. Kuhn proposed a physical therapy protocol based on a systematic review of the best available evidence for exercise in the treatment of impingement syndrome, which has been shown to be effective in Level 1 and 2 studies<sup>205</sup>.

### **2.3.2.2 Oral Non-steroidal anti-inflammatory drugs (NSAIDs)**

In the primary health care setting treatment is frequently initiated with the prescription of a NSAID. Various NSAIDs have been used in the treatment of rotator cuff problems<sup>210-212</sup>. NSAIDs are thought to act by inhibiting prostaglandin synthesis, relieving pain and suppressing the inflammatory process<sup>213</sup>. A systematic review of 19 randomised clinical trials (RCTs) in the use of NSAIDs for shoulder pain showed that NSAIDs are useful but only in the short

term<sup>213</sup>. The tolerability of oral NSAIDs varies considerably between patients, and is frequently accompanied by adverse reactions, mostly of a gastrointestinal nature but also an increase in the risk of vascular events<sup>213,214</sup>. Parenteral NSAID preparations are rarely used due to concerns about local irritation and poor tolerability<sup>215</sup>.

### **2.3.2.3 Sub-acromial injections**

Subacromial corticosteroid injection is a common first line intervention for treatment of rotator cuff problems<sup>201,216</sup>. Corticosteroids are thought to work due to its anti-inflammatory properties<sup>217</sup>. Despite many RCTs of corticosteroid injections for shoulder pain, their small sample sizes, variable methodological quality, heterogeneity in terms of population studied, injection modality employed and choice of comparator means that there is little overall evidence to guide treatment<sup>201,218</sup>. Moreover, there are concerns about potential side effects with corticosteroid injections like dermal atrophy, infection, collagen necrosis, tendon weakening and rupture<sup>219,220</sup>. A recent Cochrane review on the subject concluded that subacromial corticosteroid injection for rotator cuff disease may be beneficial although their effect may be small and not well-maintained<sup>201</sup>.

### **2.3.3 Operative treatment**

Operative treatment is considered if conservative treatment fails and the patient has persistent symptoms of pain and disability and is willing to undergo surgery<sup>221</sup>. Operative procedures can range from subacromial decompression (SAD) with or without acromioplasty to repair of the torn rotator cuff tendons<sup>222</sup>. Surgical techniques have evolved from all open repairs to all arthroscopic repairs with arthroscopic surgery being the most commonly used. Arthroscopy

offers advantages over open procedure and recent advances in equipment and techniques have now made it the procedure of choice.

Surgery performed arthroscopically requires less surgical dissection as the deltoid muscle fibres are left intact, resulting in less postoperative morbidity and discomfort. In most instances the procedure can be performed on an outpatient basis<sup>223</sup>. Arthroscopy allows concomitant examination of the glenohumeral joint as well as any associated pathology, such as labral tears, lesions resulting from instability, partial tears of the biceps tendon, and partial thickness tears of either surface of the rotator cuff<sup>223</sup>. It is also possible to examine and if necessary debride or excise the acromioclavicular joint with an arthroscopic procedure.

#### ***2.3.3.1 Subacromial decompression and acromioplasty***

Subacromial decompression (SAD) and acromioplasty are the most commonly performed surgical procedures to treat symptoms of impingement in the absence of a full-thickness tear of the rotator cuff and has been shown to be very effective in relieving the symptoms<sup>55,199,224,225</sup>. This treatment is based on Neer's theory that abnormal acromial morphology is the initiating factor for rotator cuff dysfunction and eventual tearing<sup>9,55</sup>.

However, studies have failed to find any evidence that surgical treatment is superior to conservative treatment or that one particular surgical technique is superior to another to treat subacromial impingement<sup>226,227</sup>. Gebremariam et al<sup>226</sup> looked at five RCTs reporting on various surgical techniques. They found no evidence for the superiority of subacromial decompression versus conservative

treatment in the short, medium or long term. Tashjian et al<sup>227</sup> reviewed 13 RCTs of surgical interventions in subacromial impingement and came to the conclusion that no technique is convincingly better than another or than conservative intervention.

In subacromial decompression, inflamed and thickened bursal tissue is removed from the subacromial space using a soft tissue shaver and electrocautery<sup>225</sup>. An acromioplasty is indicated if an acromial hook or spur is present or if there is evidence of abrasion on the under surface of the acromion<sup>225,228</sup>. During acromioplasty, the coracoacromial ligament is released and the prominent antero-inferior part of the acromion is resected leaving a flat undersurface<sup>55,228</sup>.

Small partial thickness tears involving less than 50% of tendon thickness can be successfully treated with SAD and debridement of the tendon<sup>229-231</sup>. SAD and acromioplasty are also considered an integral part of rotator cuff repair to allow space for the repair and the fixed tendon<sup>232</sup>. Recent evidence suggests that clinical outcomes after acromioplasty were not significantly different from subacromial decompression alone, and acromioplasty may not be necessary in the operative treatment of patients with small to medium-sized rotator cuff tears in the absence of acromial spurs<sup>232-234</sup>.

#### ***2.3.3.2 Rotator cuff debridement and repair***

Debridement of the rotator cuff with or without subacromial decompression is an effective long-term treatment for partial-thickness tendinosis or tears of the rotator cuff<sup>224,229-231,235</sup>. For high-grade partial thickness rotator cuff tears, tendon repair has been shown to be a reliable method with positive outcomes

reported for transtendon, transosseous, and tear-completion methods, with no significant difference noted between these surgical techniques<sup>236-240</sup>. In general terms, the available evidence suggest that tears that involve less than 50% of the tendon can be treated with good results by debridement of the tendon with or without a formal acromioplasty but for tears greater than 50%, surgical intervention focusing on repair has been successful<sup>241</sup>.

Open<sup>180,181,242,243</sup>, mini-open<sup>244-246</sup> and arthroscopic<sup>223,247-249</sup> repair of full thickness rotator cuff tears has been shown to result in good to excellent outcomes in terms of functional improvement and pain relief. Even patients who are aged 65 years or over with a massive full-thickness rotator cuff tear can be expected to have a good functional outcome and pain relief after repair<sup>250,251</sup>. Besides, it has been shown that rotator cuff repair for full-thickness tears produces net societal cost savings for patients under the age of sixty-one years and greater QALYs for all patients<sup>252</sup>.

There has been an evolution in available repair methods for full thickness rotator cuff tears, with transosseous repairs being augmented or replaced by single or double rows of suture anchors, and by suture bridge techniques. In spite of the improved biomechanical performance offered by the newer repair methods, re-tears are reported to happen in around 25%, associated with increased tear size and older age<sup>253-257</sup>. A systematic review on the effect of rotator cuff repair method and surgical approach on the re-tear rate found a significantly lower re-tear rate for double-row repairs (for all tears greater than 1 cm) but found no difference between arthroscopic and nonarthroscopic

approaches for any repair method<sup>258</sup>. Biologic approaches using growth factors, stem cell therapy and tissue engineering are being tried to enhance rotator cuff healing after surgery but are still in its infancy<sup>259</sup>. In patients with massive irreparable rotator cuff tears an allograft may be used to reduce pain and improve function<sup>260</sup>. Recently, a committee sponsored by the American Academy of Orthopaedic Surgeons published a clinical practice guideline summary regarding the management of rotator cuff tears<sup>261</sup>.

## 2.4 Conclusion

Rotator cuff pathology is a common condition about which there is still much to learn. Conservative treatment in the form of physiotherapy, NSAIDs and subacromial corticosteroid injections are the first line of management for rotator cuff pathology and are successful in most patients. NSAIDs have strong anti-inflammatory properties but have the potential to cause serious gastro-intestinal side effects when taken orally. There are concerns about the undesirable side effects of subacromial corticosteroid injections including on tendon integrity and tendon healing. These risks are amplified if multiple subacromial corticosteroid injections are administered. There is an argument to use a subacromial NSAID injection which could avoid or minimise the potential side effects mentioned earlier. Injectable NSAIDs have rarely been used around the shoulder due to concerns about local reactions and poor tolerability and therefore their efficacy in treating rotator cuff pathology is unknown. My aim was to conduct a trial to compare the efficacy of a subacromial NSAID injection with a subacromial corticosteroid injection in patients with rotator cuff pathology, as measured by

improvement in shoulder specific outcome scores. I designed a double blind randomised controlled trial to compare the efficacy of a single subacromial injection of 20mg of tenoxicam (NSAID) with 40mg of methylprednisolone (corticosteroid) as measured by Constant Shoulder score (primary outcome measure), six weeks after the injection.

As I was conducting the trial, I recognised that there were unresolved diagnostic challenges, especially in diagnosing partial thickness tears on ultrasound. Plain radiographs give some information about the cuff and surrounding structures but MRI or USG is required to get detailed information about the rotator cuff. USG has many advantages but is less sensitive in detecting partial thickness tears than full thickness tears. An audit of our own practice comparing preoperative ultrasonography findings with findings at arthroscopy in one hundred consecutive shoulders, has shown that the sensitivity for detecting full thickness tears by ultrasonography was 100% which falls to 83% for detecting partial thickness tears. These results were presented as a poster (Appendix A) at the annual conference of the British Elbow and Shoulder Society (BESS) and the American Academy of Orthopedic Surgeons (AAOS). Knowledge of the ultrasound dimensions of a normal rotator cuff will be helpful in diagnosing a pathologic cuff, particularly partial thickness tears. A detailed review of the literature did not reveal any studies documenting the dimensions of a normal rotator cuff in a young healthy population using ultrasonography. My aim was to document the normal rotator cuff dimensions in volunteers under the age of forty with asymptomatic shoulders in an observational study using ultrasonography. The study will also explore any correlation between the

measurements and the sex, height, weight and hand dominance of the subjects.

Further, I developed an interest in exploring factors associated with pathology of the rotator cuff. There is now a good body of evidence to suggest that rotator cuff pathology is less likely to be caused by extrinsic factors but more likely that pathology is initiated intrinsically within the tendon, with the changes in the surrounding structures being a secondary feature. A literature review by Hegedus et al on the relationship between vascularity and tendon pathology in the rotator cuff have found divergent views with little agreement on the results<sup>20</sup>. In addition, vascularity of the rotator cuff also plays an important role in the rehabilitation and surgical interventions that are chosen to treat cuff pathology. They concluded their review by suggesting that further larger sample, in-vivo, Doppler studies comparing normal and the spectrum of pathological cuffs are needed to solidify the results regarding the presence of a critical zone and the effect of hypo/hypervascularity on age and degeneration<sup>20</sup>.

When conservative methods fail, arthroscopy has changed rotator cuff surgery considerably. This allows minimal access surgery, although successful repair of the torn tendon is still a challenge. Despite advances in surgical techniques, equipment and materials and the adaptation of evidence-based post-operative physiotherapy regimes, the tendon repair failure rate still remains high. While further work needs to be done to establish the important factors that allow successful healing of the tendon, it is highly likely that micro-vascular blood flow of the tendon will be an important factor in tendon healing and the outcome of any surgical intervention and further work to understand this is warranted. My plan was to conduct a study using an intraoperative laser Doppler probe to measure the

microvascular blood flow in rotator cuffs of patients undergoing arthroscopic shoulder surgery. The study was designed to measure blood flow in different regions of the cuff and to look for variations of blood flow in normal rotator cuffs as well as for differences in microvascular blood flow between normal rotator cuff and rotator cuffs with tendinopathy, partial thickness tears or full thickness tears.

In summary, my period of research about the management of rotator cuff pathology started with a randomised controlled trial of subacromial injections comparing NSAID with a corticosteroid. As I was conducting the trial, I developed an interest in exploring unresolved issues related to diagnosis and pathogenesis of rotator cuff tears. This led me to conduct two further studies – ultrasound dimensions of rotator cuff in young asymptomatic volunteers and pattern of microvascular blood flow in normal and pathological rotator cuffs. These studies are presented in the thesis in the order they were conducted.

## **2.5 Research Questions**

This review has led me to formulate the following research questions which forms the basis for my thesis

1. Can subacromial injection of a NSAID provide equal or better outcome compared to a subacromial corticosteroid injection as measured by functional outcome scores?
2. What are the normal dimensions of rotator cuff in asymptomatic young adults, as measured by ultrasonography?

3. Can intra-operative ultrasound provide accurate description of rotator cuff tears?
4. Does the normal rotator cuff in living humans have a uniform blood flow throughout the tendon and is there a difference in microvascular blood flow between normal rotator cuff and rotator cuffs with tendinopathy, partial thickness tears or full thickness tears?

### **Chapter 3 A double-blind randomised controlled study comparing subacromial injection of tenoxicam or methylprednisolone in patients with subacromial impingement**

#### Summary:

*In this chapter, the efficacy of the two commonly used groups of drugs in the treatment of rotator cuff pathology is discussed. The rationale and feasibility for using a subacromial NSAID injection is explored and its efficacy compared with a subacromial corticosteroid injection in a double blind randomised controlled trial.*

#### Declarations:

*Dr Nicholas Parsons provided support for statistics and Mr Steve Drew administered the subacromial injection*

#### This work has been published

*Karthikeyan S, Kwong HT, Upadhyay PK, Parsons N, Drew SJ, Griffin D: A double blind randomised controlled study comparing subacromial injection of tenoxicam or methylprednisolone in patients with subacromial impingement.*

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## 3.1 Introduction

### 3.1.1 Background

Neer described subacromial impingement as a clinical condition that produces pain in the lateral region of the deltoid, when the affected extremity is forcibly elevated while the scapula is stabilized in the standing position<sup>55</sup>. It indicates a pathologic process between the roof and floor of the subacromial space leading to impingement of rotator cuff tendons and subacromial bursa between the humeral head and structures that make up the coracoacromial arch. The etiology for this syndrome is diverse<sup>262</sup>. It is one of the most common musculoskeletal problems leading to shoulder pain and consequent functional limitation<sup>9</sup>.

The exact pathophysiology causing the subacromial impingement syndrome is not completely known and therefore, based on empirical evidence a wide spectrum of treatment options has been proposed<sup>263</sup>. These range from conservative measures like rest, activity modification, physical therapy, anti-inflammatory drugs to surgical options like arthroscopic or open subacromial decompression and even total acromionectomy<sup>47,55,198,199,210,264</sup>. Although drugs such as non-steroidal anti-inflammatories (NSAIDs) and subacromial injections of local anaesthetic or corticosteroids are among the most common treatment options in the management of subacromial impingement syndrome, their use has remained controversial owing to conflicting evidence in the literature supporting their efficacy<sup>201,211,265,266</sup>.

Subacromial injection of corticosteroid is one of the most common non-operative interventions for the treatment of impingement syndrome and several studies have shown it to be effective in providing symptomatic relief<sup>201,216,267</sup>. The precise mechanism by which corticosteroid injections provide symptomatic relief in subacromial impingement syndrome is not well understood. Possible therapeutic mechanisms include anti-inflammatory effects, relaxation of reflex muscle spasm, influence of local tissue metabolism, pain relief, mechanical improvement, and even a placebo effect<sup>268</sup>.

Despite the popularity of the intervention a consensus seems to exist that there has been a lack of good trials defining the scientific basis of subacromial corticosteroid injections, and in particular quantification of its efficacy<sup>201,216,267</sup>. More important, there are potential complications associated with subacromial corticosteroid injections and these include dermal atrophy, infection including septic arthritis and abscess, collagen necrosis and tendon weakening or rupture<sup>219,220,269,270</sup>. Despite considerable research, no real alternative to corticosteroid has been offered for subacromial injections. If corticosteroids are effective because of their anti-inflammatory properties, there is an argument to try an alternative drug designed specifically as an anti-inflammatory, such as a NSAID, which might be a more effective therapeutic intervention without the potential complications associated with corticosteroids.

NSAIDs in general have potent analgesic and anti-inflammatory properties, and several have been used to treat tendonitis of the rotator cuff<sup>210-213,271-273</sup>. A systematic review has shown that although NSAIDs showed superior short-term efficacy compared to placebo, there are wide variations in the type of

NSAID, the dose, frequency and mode of administration and the duration of treatment<sup>213</sup>. The study found no conclusive evidence in favour of a particular NSAID with respect to efficacy or tolerability. NSAIDs are most commonly administered as an oral preparation but the tolerability of oral NSAIDs varies considerably between patients, and is frequently accompanied by severe gastrointestinal side effects, which forces a proportion of patients to discontinue treatment<sup>213,214</sup>. NSAIDs are not often used for intralesional or local injection because of insufficient data, short duration of action, local irritation and poor tolerability<sup>215</sup>.

Tenoxicam, a NSAID belonging to the oxicam group, addresses some of these concerns. Tenoxicam is available as a long acting, water soluble preparation for injection without irritant preservatives or emulsifying agents such as benzyl alcohol and propylene glycol, which are known to cause local irritation and sometimes necrosis<sup>215</sup>. Tenoxicam has been administered as a local, intramuscular or intravenous injection and well tolerated both systemically and locally by patients<sup>215,274,275</sup>. Itzkowitch et al<sup>215</sup> found that periarticular injection of tenoxicam was effective in treating rotator cuff tendinitis in a randomised placebo-controlled study.

Our aim was to conduct a double-blind randomised controlled trial to evaluate the efficacy of a single subacromial injection of NSAID in improving shoulder function and compare it to a single subacromial injection of corticosteroid in patients with subacromial impingement.

Vischer<sup>276</sup> conducted a review on the efficacy and tolerability of Tenoxicam. They reviewed open studies providing initial data on the efficacy and safety, double-blind studies versus placebo to assess efficacy and comparative studies assessing different doses of Tenoxicam in comparison with reference drugs like indomethacin, naproxen, ibuprofen, diclofenac and piroxicam. They state that the efficacy of Tenoxicam has been demonstrated in double-blind comparative studies against placebo, and dose-finding studies have found the optimal dose to be 20 mg in patients with post-operative pain, ankylosing spondylitis, acute tendinitis and rheumatoid, osteo or gouty arthritis. It was found to be well tolerated both in short-term and long-term studies. The types of side-effects encountered were mainly gastrointestinal disturbances, followed in frequency by skin rashes. All side-effects were generally mild and reversible<sup>276</sup>. Tenoxicam has the advantages of high efficacy coupled with low toxicity and the pharmacokinetic properties of extensive metabolic degradation prior to elimination and long half-life<sup>277</sup>. Tenoxicam has been used intra-articularly for post-operative pain relief after knee arthroscopy and found to be effective<sup>278,279</sup>. Besides, locally administered tenoxicam was found to be well tolerated and effective in alleviating pain and improving shoulder mobility<sup>215</sup>. This study provided evidence and established that local NSAID therapy and in particular tenoxicam is a viable treatment for impingement syndrome. It seemed appropriate to use 20mg tenoxicam (Mobiflex, Roche, Welwyn Garden City, United Kingdom) as the preferred NSAID in the trial.

To choose the appropriate corticosteroid for the trial, we conducted a survey among the rheumatologists and the orthopaedic surgeons in our trust about their preferred drug for use as a subacromial injection. A significant majority used 40 mg of methylprednisolone (Depomedrone, Pfizer, Puurs, Belgium) along with 5 ml of 1% lignocaine, while a few used triamcinolone. No one used a NSAID for subacromial injections. Therefore, Depomedrone was chosen to represent the corticosteroid arm of the trial.

### 3.1.2 Methylprednisolone

Methylprednisolone is a synthetic glucocorticoid drug. Glucocorticoids are a class of steroid hormones mainly synthesised in the zona fasciculata of the adrenal cortex. The name glucocorticoid (**glucose + cortex + steroid**) is derived from its role in the regulation of glucose metabolism, its production in the adrenal cortex, and its steroidal structure (Figure 3-1). Glucocorticoids are potent anti-inflammatories regardless of the cause of inflammation and are widely used for the suppression of inflammation in chronic inflammatory diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease and autoimmune diseases<sup>280</sup>.

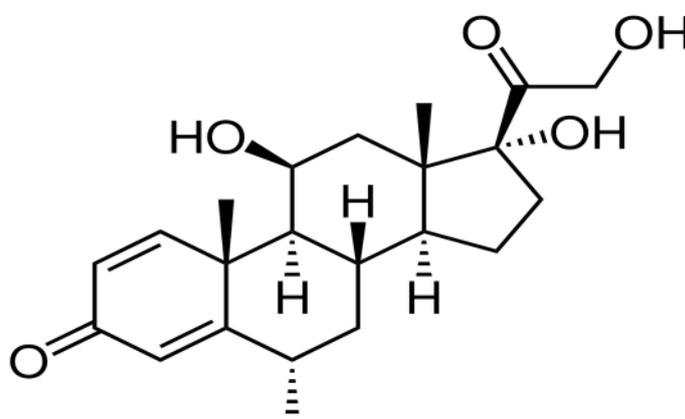


Figure 3-1: Chemical structure of methylprednisolone

### **3.1.2.1 Mechanism of action**

Glucocorticoids act by binding to the glucocorticoid receptors which is expressed in virtually all cells<sup>280,281</sup>. The activated glucocorticoid receptor complex controls inflammation by increasing the transcription of anti-inflammatory proteins and decreasing the transcription of pro-inflammatory proteins. Glucocorticoids increase the synthesis of lipocortin-I, a protein that suppresses phospholipase A, (PLA), thereby blocking eicosanoid production, and inhibiting various leucocyte inflammatory events like epithelial adhesion, emigration, phagocytosis and chemotaxis. They also down regulate the transcription of several pro-inflammatory cytokines including IL-18, IL-2, IL-3, IL-6, IL-11, TNF- $\alpha$ , GM-CSF and other chemical mediators (chemokines) that attract inflammatory cells to the site of inflammation<sup>280,281</sup>.

### **3.1.2.2 Indications**

Like most adrenocortical steroids, methylprednisolone is typically used for its anti-inflammatory and immunosuppressive properties. It is available as methylprednisolone, methylprednisolone acetate and methylprednisolone sodium acetate. It is commonly used to treat

- Inflammatory conditions like rheumatoid arthritis, psoriatic arthritis, polymyalgia rheumatica, crohn's disease and ulcerative colitis
- Severe allergic conditions like bronchial asthma, acute bronchitis and allergic rhinitis
- Autoimmune disorders like systemic lupus erythematosus
- Chronic skin conditions like pemphigus, dermatitis herpetiformis and severe psoriasis.

- Allergic and inflammatory conditions of the eye including that of conjunctiva, iris and optic nerve.
- High dose methylprednisolone is used in the early treatment of severe spinal cord injuries.

### 3.1.2.3 Contraindications and cautions

Methylprednisolone is contraindicated in patients who have previously shown hypersensitivity to the product or its constituents. It is contraindicated in patients with systemic fungal infections. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and their severity and therefore should be used with caution. Treatment should be monitored more closely in patients who have been exposed to someone with chickenpox or shingles but they themselves have not already had these illnesses. It should be used with caution in patients with a history of depression, bipolar disorder, diabetes, glaucoma and epilepsy.

### 3.1.2.4 Adverse effects

Current glucocorticoid drugs that are being used act non-selectively and therefore have a wide range of effects, including changes to metabolism and immune responses. Long-term use of methylprednisolone, as with all corticosteroids, can be associated with side effects in all tissues and systems<sup>281</sup> (Table 3-1).

Tissue/System	Side effects
<b>Adrenal gland</b>	Adrenal atrophy, Cushing's syndrome
<b>Cardiovascular system</b>	Hypertension, Thrombosis, Vasculitis, Pulmonary embolism
<b>Central nervous system</b>	Changes in behaviour, memory and mood, cerebral atrophy

<b>Gastrointestinal tract</b>	Peptic ulceration, bleeding and pancreatitis
<b>Immune system</b>	Immune suppression, activation of latent viruses
<b>Metabolism</b>	Gluconeogenesis, insulin resistance and hyperglycaemia
<b>Musculoskeletal system</b>	Muscle atrophy, osteoporosis, bone necrosis, growth retardation
<b>Eyes</b>	Cataracts, glaucoma
<b>Skin</b>	Atrophy, delayed wound healing, dermatitis
<b>Reproductive system</b>	Hypogonadism, delayed puberty

**Table 3-1: Adverse effects of glucocorticoids**

The most serious side effect occurs when the externally administered drug methylprednisolone cause the adrenal glands to cease natural production of cortisol. Sudden withdrawal of the drug after this occurs can result in a condition known as Addisonian crisis, which if untreated can be fatal<sup>282</sup>.

### **3.1.2.5 Pharmacokinetics**

Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. The plasma protein binding of methylprednisolone in humans is approximately 77%. In humans, methylprednisolone is metabolized in the liver to inactive metabolites; the major ones are 20 $\alpha$ -hydroxymethylprednisolone and 20 $\beta$ -hydroxymethylprednisolone. The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours<sup>283</sup>. No dosing adjustments are necessary in renal failure.

Methylprednisolone acetate is less soluble than methylprednisolone.

### **3.1.2.6 Preparation**

The preparation used in the study was Depo-medrone 40 mg/ml. It contains methylprednisolone acetate 40 mg/ml as a sterile aqueous suspension. The

product also contains polyethylene glycol, sodium chloride, myristyl-gamma-picolinium chloride and sterile water for injections. It can be administered by any of the following routes: intramuscular, intra-articular, periarticular, intrabursal, intralesional and into the tendon sheath. The product is manufactured by Pfizer (Pfizer, Puurs, Belgium).

### 3.1.3 Tenoxicam

Tenoxicam a thieno-thiazine derivative is a non-steroidal anti-inflammatory drug (NSAID) belonging to the class oxicams (Figure 3-2). It has anti-inflammatory, analgesic and antipyretic effects. It has been shown on clinical trials that the efficacy of tenoxicam is at least equivalent to that of other NSAIDs<sup>284</sup>. It is at least as well tolerated as piroxicam and probably better tolerated than diclofenac, indomethacin and ketoprofen<sup>284</sup>. Tenoxicam offers certain advantages compared with other NSAIDs as it can be conveniently administered once daily and dosage adjustment is not required in the elderly or in patients with renal or hepatic impairment.

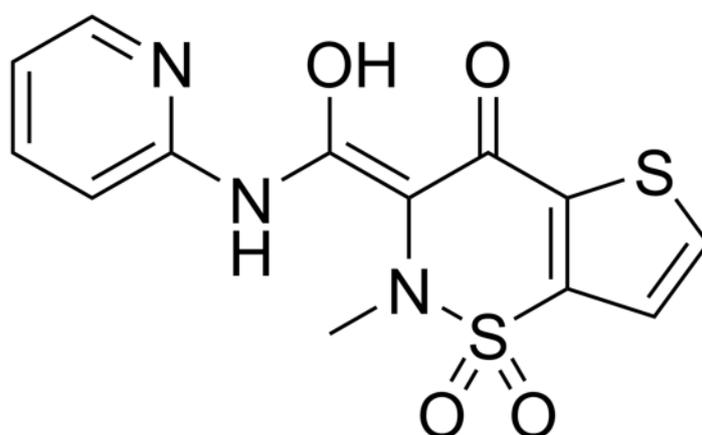


Figure 3-2: Molecular structure of tenoxicam

### **3.1.3.1 Mechanism of action**

Tenoxicam is an inhibitor of prostaglandin biosynthesis both in vitro and in vivo. Its primary mode of action is the inhibition of the cyclooxygenase pathway, which is involved in the biosynthesis of prostaglandins and thromboxanes from arachidonic acid. Cyclooxygenase (COX) is the pivotal enzyme involved in the biosynthesis of prostaglandins. It exists in two isoforms, COX-1 (important for physiological functions) and COX-2 (involved in inflammation)<sup>285,286</sup>. The constitutive isoform of COX, COX-1, has clear physiologic functions. Its activation leads, for instance, to the production of prostacyclin, which, when released by the gastric mucosa, is cytoprotective<sup>287</sup>. The inducible isoform, COX-2, is induced in a number of cells by pro-inflammatory stimuli<sup>286</sup>. It therefore appears that inhibition of COX is responsible for both the therapeutic effects (inhibition of COX-2) and side effects (inhibition of COX-1) of NSAIDs<sup>285,286</sup>. NSAIDs, which inhibit the COX-2 isomer selectively, are likely to possess maximal anti-inflammatory efficacy combined with less gastrointestinal and renal toxicity. Its ability to inhibit leucocyte functions, including phagocytosis and histamine release, and to promote the scavenging of oxygen radicals may contribute to its anti-inflammatory activity<sup>284</sup>.

### **3.1.3.2 Indications**

Like other NSAIDs, tenoxicam can be used in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and extra-articular inflammations such as tendinitis, bursitis and peri-arthritis of the synovial joints. Studies have shown that the currently recommended dosage of 20mg once daily provides the best balance between efficacy and tolerability<sup>284</sup>.

### **3.1.3.3 Contraindications**

Tenoxicam is contraindicated in patients who have previously shown hypersensitivity to the drug. It should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by other NSAIDs. Tenoxicam should not be administered to patients with active peptic ulcer or active inflammatory diseases of the gastrointestinal tract or with history of gastrointestinal bleeding or perforation related to previous NSAIDs therapy. It is contraindicated in patients with severe heart failure, hepatic failure or renal failure.

### **3.1.3.4 Adverse reactions**

Tenoxicam is generally well tolerated with most side effects being mild to moderate in intensity and only transient. The most common adverse reactions encountered are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe followed by cutaneous (rash, pruritus) and nervous system (headache, dizziness) complaints<sup>284</sup>. Other gastrointestinal side effects that have been observed with tenoxicam include dyspepsia, nausea, constipation, abdominal pain and diarrhoea. In rare cases, tenoxicam and other NSAIDs can contribute to thrombotic events, Stevens-Johnson syndrome, and Toxic Epidermal Necrolysis (TEN). Care should be taken to regularly monitor patients to detect possible interactions with concomitant therapy and to review renal, hepatic and cardiovascular function, which may be potentially influenced by tenoxicam.

### **3.1.3.5 Pharmacokinetics**

Tenoxicam is rapidly and completely absorbed following oral administration. The bioavailability of the drug is essentially 100%. It is highly bound to plasma proteins (98 to 99%), primarily albumin and rapidly distributed throughout the body<sup>277</sup>. The average time to achieve peak plasma concentrations is 1 to 2.6 hours fasting and 4 to 6 hours postprandial<sup>284</sup>. Tenoxicam is eliminated slowly from the plasma with a half-life of 60 to 75 hours, permitting once daily doses<sup>277</sup>. Peak concentrations of tenoxicam in synovial fluid are approximately half those in plasma. Approximately two thirds of tenoxicam is excreted in the urine, mainly as the pharmacologically inactive metabolite, 5-hydroxytenoxicam, and the remainder in the bile much of it as glucuronide conjugates of hydroxy-metabolites.

The absorption, distribution, and elimination kinetics of tenoxicam are independent of dose<sup>288</sup>. The bioavailability of tenoxicam is unaffected by age, gender, renal or hepatic impairment, and rheumatic disease states. Due to the rapid absorption and terminal half-life of the drug its plasma concentration profile after oral administration was very similar to that following intravenous dosing. The pharmacokinetic characteristics of tenoxicam allows the entire daily dose to be administered in one single portion<sup>277</sup>.

### **3.1.3.6 Preparation**

Tenoxicam is available in tablet form for oral administration or as an injection for parenteral administration. The preparation used in the trial was Mobiflex injection. The Mobiflex vials contain 20mg sterile tenoxicam and inactive

ingredients: mannitol, ascorbic acid, disodium edetate, sodium hydroxide, tromethamine and hydrochloric acid as a lyophilized powder for dissolving in solvent. The solvent in the ampoule contains water for injection. The product license holder and the manufacturer responsible was Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom.

## **3.2 Study design for double blind randomised control trial**

### **3.2.1 Research question**

In patients with clinically diagnosed subacromial impingement syndrome, does a single subacromial injection of 20 mg of tenoxicam provide equal benefit compared to a single subacromial injection of 40 mg of methylprednisolone as measured by changes in Constant shoulder score at six weeks?

### **3.2.2 Ethics approval**

The study protocol was approved by the local research ethics committee (Coventry and Warwickshire) and by the Research and Development Department at the Coventry and Warwickshire hospital. For the use of tenoxicam as subacromial injection in this study, the clinical trial licence for doctors (MLA 162, DDX) was obtained from the Medicines Control Agency.

### **3.2.3 Outcome assessment**

#### **3.2.3.1 Primary outcome measure**

The primary outcome measure was the Constant Shoulder Score<sup>289</sup>, devised by Christopher Constant with help from Alan Murley. The score was first presented in a university thesis in 1986 and published in 1987. It is a functional

assessment score to assess the overall value of a normal, diseased, or treated shoulder<sup>290</sup>. In this score, points are allocated for subjective assessments of pain (15 points) and activities of daily living (20 points), as well as objective measurements of the range of active shoulder movement (40 points) and strength of abduction (25 points). A young healthy patient can therefore have a maximum score of 100 points (Appendix: B).

Assessment for pain is made on the most severe pain felt by the patient during ordinary activities over a 24-hour period. For activities of daily living, points are allocated for undisturbed sleep, work and recreational activities and the ability to functionally use the arm up to a certain level. The 40 points allotted to movement are divided equally into forward elevation, lateral elevation, functional external rotation, and functional internal rotation. All the movements must be painless and active to gain the maximum points. Abduction strength is recorded at 90 degrees of abduction in the scapular plane, with the wrist pronated so that the hand is facing the floor. A strap is applied at the level of the wrist with the arm at maximum span. The strength measurement is repeated three times, each separated by at least a minute and the maximum value is used to calculate the score.

At present, Constant score is considered to be the most appropriate score for assessing overall shoulder function and the European Society for the Surgery of the Shoulder and the Elbow has agreed that the Constant score should be used for all presentations to the society and for all communications to the Journal of Shoulder and Elbow Surgery<sup>290</sup>.

### **3.2.3.2 Secondary outcome measures**

The Disability of the Arm, Shoulder and Hand score (DASH)<sup>291</sup> and the Oxford Shoulder score (OSS)<sup>292</sup> were used as secondary outcome measures. The former is a self-administered region-specific outcome instrument developed as a measure of self-rated upper-limb disability and symptoms. It consists primarily of a 30-item disability/ symptom scale, scored 0 (no disability) to 100. It has been validated and is shown to be useful in assessing the effectiveness of treatment of the impingement syndrome<sup>293,294</sup> (Appendix: C). The OSS is a shoulder-specific self-administered questionnaire consisting of 12 items scored on a five-point ordinal scale. Scores are summed to give a single score, with a range from 12 (best) to 60 (worst). It has been shown to be consistent, valid, reproducible, and sensitive to clinical change<sup>292</sup> (Appendix: D).

Patients were also asked about their use of oral analgesia during the study period, and gave a global assessment of their shoulder condition, rating it as much better, slightly better, no change, slightly worse or much worse.

### **3.2.4 Sample size calculation.**

A power analysis was used to calculate the required sample size. Patient numbers were calculated, assuming an approximate normal distribution for the primary outcome measure with a standard deviation of 12 points, to detect a minimal clinically important difference of ten points in the Constant Shoulder score<sup>295</sup> between treatment groups at a 5% level of significance with

80% power<sup>296,297</sup>. Allowing for some losses to follow-up (10%), this gave a minimum sample size of 25 patients for each arm of the trial.

### 3.2.5 Inclusion criteria.

All patients over the age of 18 years with a clinical diagnosis of subacromial impingement syndrome as made by an upper limb orthopaedic consultant based on history and clinical examination were considered eligible to participate in this study. Clinical features suggestive of subacromial impingement syndrome were:

- History of pain around the shoulder and/or lateral deltoid area, which worsened with overhead activity.
- Painful arc of movement on passive and/or active abduction
- Tenderness over the insertion of the cuff
- Positive Neer's sign<sup>9</sup>
- Positive Hawkins-Kennedy impingement sign.

Neer's impingement sign is elicited with the patient seated and the examiner standing behind the patient. The examiner prevents scapular rotation with one hand and passively elevates the arm in forced forward elevation, causing the greater tuberosity to impinge against the acromion and producing pain in patients with all stages of impingement<sup>9</sup>. What is commonly referred to as the Hawkins sign involves passive forward flexion of the arm to 90° and a maximal internal rotation maneuver that theoretically impinges the rotator cuff and greater tuberosity against the undersurface of the acromion and the coracoacromial ligament<sup>165</sup>. When positive, these signs are often used to make the diagnosis of impingement syndrome<sup>298</sup>.

All patients had symptoms that had been present for at least three months, and had already undergone a period of conservative therapy consisting of rest, physiotherapy and/ or oral anti-inflammatory medications. They all had an anteroposterior (AP) shoulder radiograph to rule out other causes of shoulder pain, such as arthritis of the glenohumeral or acromioclavicular joint. This was a pragmatic trial, designed to mimic the typical presentation of a patient with an impingement syndrome to an orthopaedic clinic, and therefore advanced imaging tests such as ultrasound or MRI were not considered as part of the initial evaluation.

### **3.2.6 Exclusion criteria**

Patients were excluded from the study if any of the following criteria were present:

- Evidence of other pathology causing shoulder pain, such as arthritis of glenohumeral or acromioclavicular joints, adhesive capsulitis, fracture or rotator cuff tear presenting with weakness and muscle wasting.
- Any injection in the same shoulder within the previous six months.
- Previous shoulder surgery on the same side
- Patients taking regular systemic NSAIDs or steroids, or in whom those drugs were contraindicated.
- If their shoulder condition was currently the subject of any legal proceedings or insurance claims.
- Pregnant and breastfeeding mothers.

### **3.2.7 Consent**

Patients who satisfied the inclusion criteria were approached to participate in the trial. The study's purpose, benefits, risks, questionnaires and alternative to participation were discussed with each patient. All patients recruited into the trial gave informed consent for participation in the trial. Patients not wishing to participate were treated according to existing protocols.

### **3.2.8 Randomisation and preparation of medication.**

Random numbers for allocating patients to treatment groups were generated using a computer program. Before the study started, a set of sealed, consecutively numbered envelopes containing the random allocation details for each patient was prepared by colleagues not involved in the study.

The patients were randomised to have either a single injection of 20 mg tenoxicam mixed with 5 ml 1% lignocaine, or 40 mg methylprednisolone mixed with 5 ml 1% lignocaine. The researcher prepared the injection and an independent clinic nurse kept the syringes. When a patient was recruited, the nurse was instructed to open one sealed envelope according to the individual patient's recruitment number. The nurse took one prepared syringe containing the appropriate injection according to the details inside the envelope. Two opaque labels were applied to cover the whole syringe body, so that no other person could identify the medication inside it. It was then handed back to the researcher ready for injection into the patient's affected sub-acromial space by one of the orthopaedic consultants. Throughout the preparation and follow-up, all patients, outcome assessors and treating consultants were blinded to the medication used; only the nurse who was

responsible for opening the envelope and covering the appropriate syringe with labels was aware of the treatment allocated. The independent clinic nurse discarded all unused medication at the end of each clinic.

### **3.2.9 Procedure.**

Following recruitment into the trial, each patient completed the DASH and Oxford Shoulder score and underwent an evaluation for calculating the Constant score. A hand-held goniometer was used to measure the active and passive ranges of motion (ROMs) and the abduction strength was recorded using a Nottingham Mecmesin Myometer (Atlantech Medical Device Ltd, Harrogate, United Kingdom).

Upon completion of the initial evaluation, the consultant gave the injection, using a 21-gauge needle with the covered syringe, into the patient's subacromial bursa via the anterolateral approach applying an aseptic technique. A reduction in pain of at least 50% with full active abduction ten minutes after injection (Neer's impingement test)<sup>9</sup> confirmed accurate placement of the injection in the subacromial bursa. Patients were advised to take simple analgesia if required, but to avoid any preparation containing NSAIDs. Everyone had standardised outpatient physiotherapy provided by an experienced specialist shoulder physiotherapist which was tailored to meet the needs of each patient and was aimed at correcting posture, associated muscle spasm or imbalance, posterior capsular tightness and restoring normal scapulothoracic movements.

All patients were followed up at 14 and 28 days, and the two self-reported outcome measures (OSS, DASH) were completed via telephone by the researcher. At six weeks, patients were followed up in the outpatient clinic and the primary and secondary outcome measures were collected.

### **3.2.10 Statistical analysis.**

This is a study of equivalence between two treatments. Hence, our null hypothesis was that there was no difference between the treatment groups.

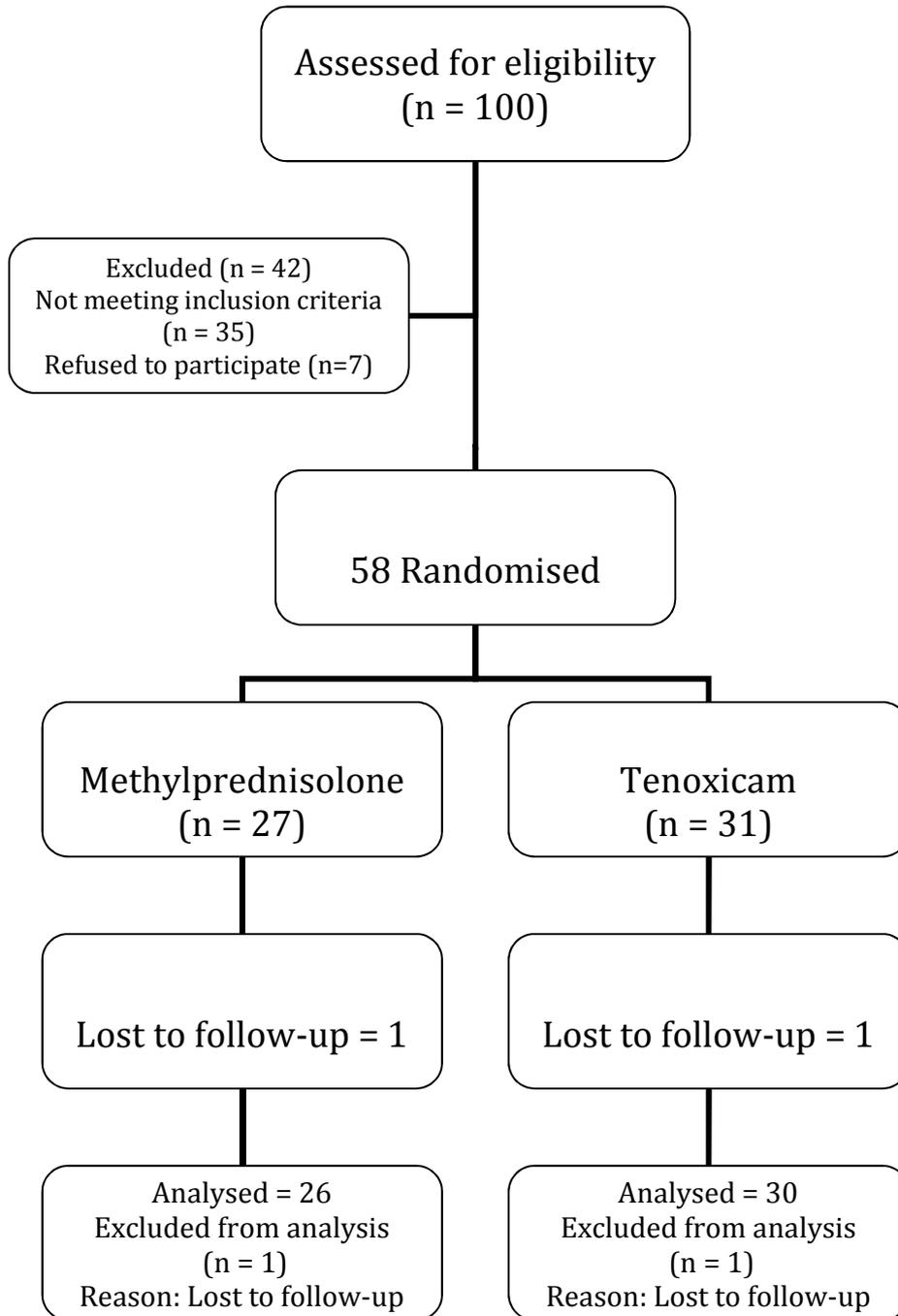
Data on the outcome scores were analysed using the non-parametric Mann-Whitney U test, and the subjective assessments of pain and shoulder function were analysed using chi-squared test. A p-value  $\leq 0.05$  was considered significant. Box plots expressed the median and the interquartile ranges (IQR) for each group. Whiskers represent 1.5 times the IQR and outliers beyond 1.5 times the IQR are represented as dots.

## **3.3 Results**

CONSORT statement<sup>299,300</sup> guidelines were used to report the trial.

### **3.3.1 Recruitment.**

Patients were recruited from a specialist upper limb clinic at the University Hospital of Coventry and Warwickshire. Over a two-year period, 100 patients were considered for participation in the study. Forty-two patients were excluded as they did not meet the criteria, while seven refused to participate. 58 patients who satisfied the inclusion and exclusion criteria and provided informed consent were enrolled in the study, of which 27 were randomised to the methylprednisolone group and 31 to the tenoxicam group (Figure 3-3).



**Figure 3-3: Flow diagram for a randomised control trial comparing a subacromial injection of methylprednisolone to tenoxicam for treating patients with subacromial impingement syndrome**

The two groups were comparable with respect to age, gender, duration of symptoms and the affected side. There were no significant differences in

shoulder scores between the two groups before the injection. These data are summarised in [Table 3-2](#).

Characteristic	Treatment group	
	Steroid (n=27)	Tenoxicam (n=31)
<i>Mean age in years (range)</i>	60 (36-88)	58 (36-75)
<i>Gender (M:F)</i>	16:11	16:15
<i>Mean duration of symptoms in Months (range)</i>	8 (2-12)	10 (2-12)
<i>Side</i>		
<i>Dominant</i>	16	15
<i>Non-dominant</i>	11	16
<i>Median Constant score (range)</i>	44.0 (18 to 85)	41.5 (25 to 92)
<i>Median DASH score (range)</i>	45.0 (11.7 to 89.2)	36.7 (4.2 to 64.2)
<i>Median Oxford shoulder score (range)</i>	32.5 (21 to 52)	32.0 (17 to 48)

**Table 3-2: Study patient baseline characteristics for the Steroid and NSAID groups.**

Two patients (one in each group) were lost to follow-up. The remaining 56 were seen for review six weeks after injection.

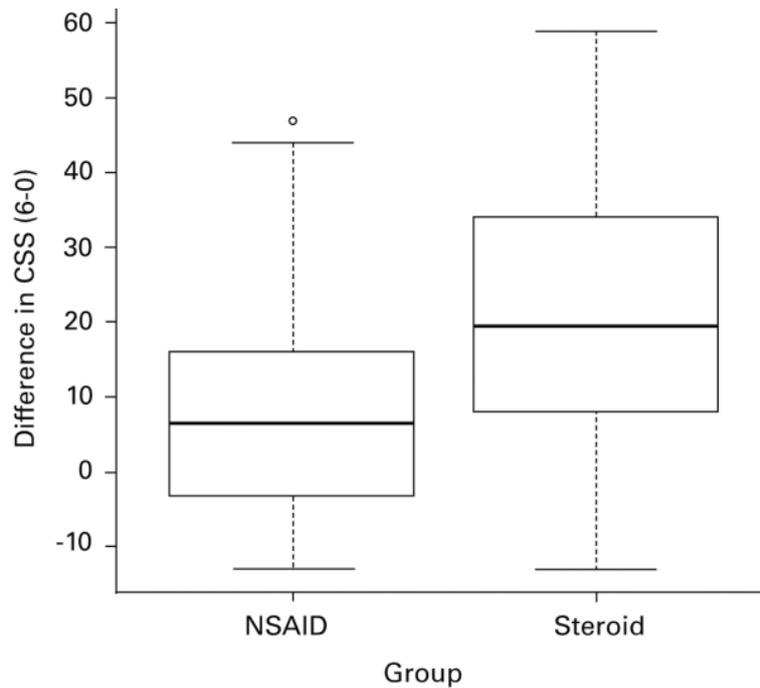
### 3.3.2 Primary outcomes.

The baseline median Constant score for patients treated with steroid was 44 points just before they had their subacromial injection and this improved to 73.5 points at the time of their final review at 6 weeks. For patients treated with NSAID, the baseline median Constant score was 41.5 points, which improved to 54 points at six weeks (Table 3-3).

Time after injection	Treatment group	
	Steroid	Tenoxicam
<i>0 week</i>	44.0 (33.5 to 65.5)	41.5 (35.5 to 62.5)
<i>6 weeks</i>	73.5 (56.0 to 81.8)	54.0 (36.6 to 74.8)

**Table 3-3: Median (interquartile range) of Constant Shoulder score at baseline and six weeks. Patients in the steroid group had significantly higher scores (Mann-Whitney,  $p = 0.003$ ) than the non-steroidal anti-inflammatory group at six weeks.**

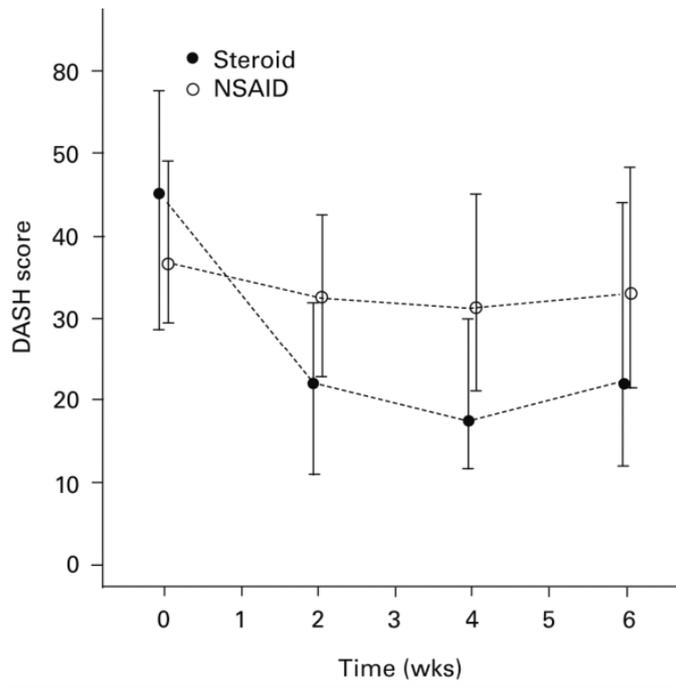
Patients in both treatment groups showed an improvement in their Constant scores six weeks after the injection. The improvement was more pronounced in the steroid group. The median improvement in the Constant score at six weeks was 19.5 points (IQR 8.75 to 33) for patients in the steroid group and 6.5 points (IQR -3 to 15.75) for patients in the non-steroidal group (Figure 3-4). This difference was found to be statistically significant (Mann-Whitney,  $p = 0.003$ ). In all, 25 of the 26 patients who were followed up in the steroid group showed an improvement in the Constant score, whereas in the non-steroid group 21 patients showed an improvement and nine a reduced score after six weeks.



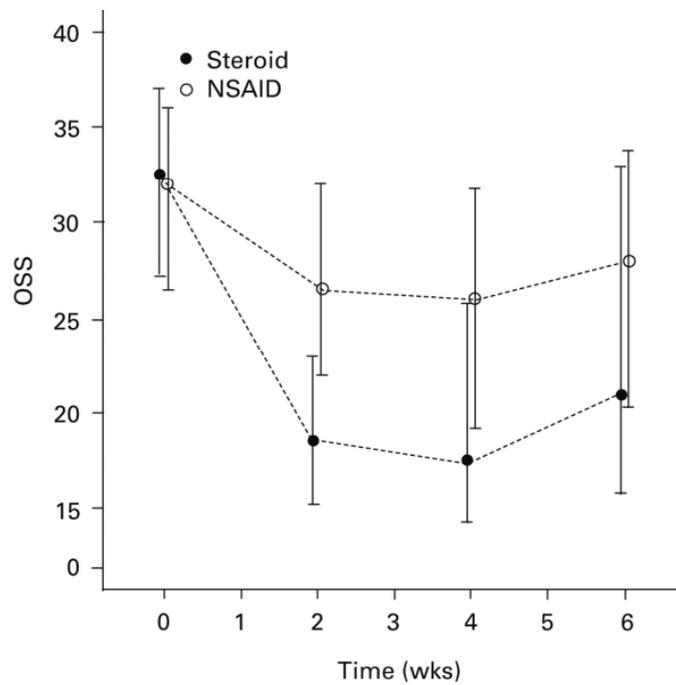
**Figure 3-4: Box plot showing median (bold line) and inter-quartile range (box) and outliers (dashed lines and points) for improvement in the Constant Shoulder Score (CSS) at 6 weeks for each group.**

### 3.3.3 Secondary outcomes.

Patients in both treatment groups were contacted by the researcher at 2 weeks and 4 weeks after the injection and completed the DASH score and the OSS over the telephone. In addition, they completed both the questionnaires just before they had their subacromial injections and at the time of final assessment at 6 weeks in the clinic. Patients in the two study groups showed improvement in both the DASH and the OSS following the injection and this improvement persisted throughout the study period (Figure 3-5 and Figure 3-6).



**Figure 3-5: Chart showing changes in the median Disability of Arm Shoulder and Hand (DASH) score from baseline to six weeks for the steroid and non-steroidal anti-inflammatory (NSAID) groups. Patients in the steroid group had significantly better scores than the NSAID group at two, four and six weeks. Bars show the interquartile ranges.**



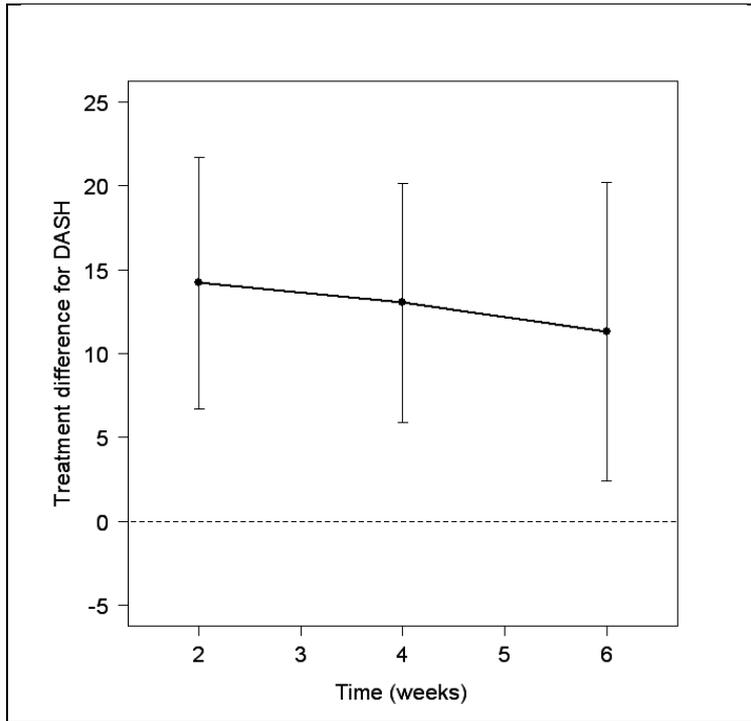
**Figure 3-6: Chart showing changes in the median Oxford Shoulder Score (OSS) from baseline to six weeks for the steroid and non-steroidal anti-inflammatory (NSAID) groups. Patients in the steroid group had significantly better scores than the NSAID group at two and four weeks. Bars show the interquartile ranges.**

Patients in the steroid group showed much greater improvement than patients in the NSAID group and this difference was found to be significant throughout the study period at two, four and six weeks after the injection for DASH, while for OSS the difference was found to be significant at 2 and 4 weeks but did not reach statistical significance at 6 weeks. The results are given in Table 3-4 and illustrated in Figure 3-5 and Figure 3-6.

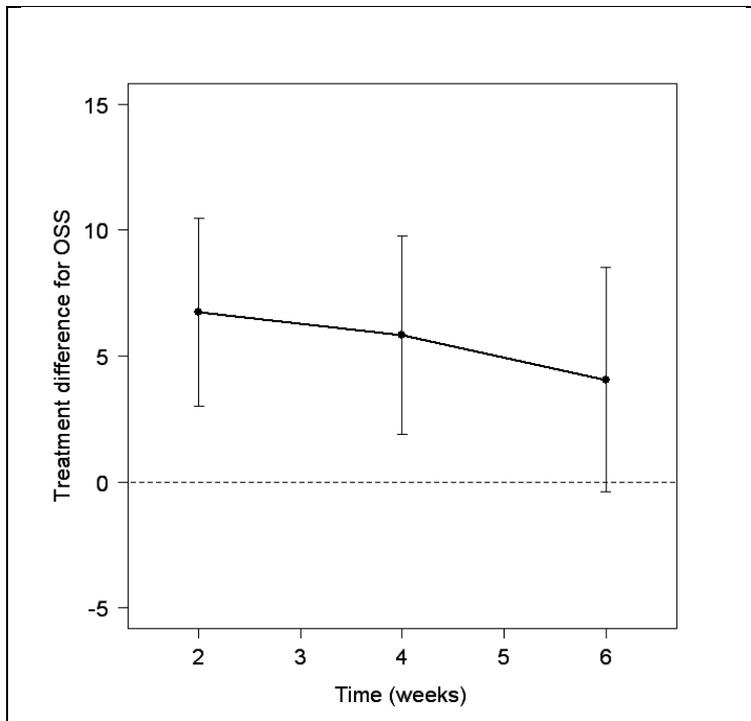
Time after injection	Score	Treatment group		p-value
		Steroid	NSAID	
2 weeks	DASH	19.6 (11.1 to 28.5)	4.6 (0.2 to 8.4)	<0.001*
	OSS	13.0 (8.0 to 15.8)	3.5 (1.3 to 10.0)	<0.001*
4 weeks	DASH	16.7 (12.5 to 28.8)	6.7 (-0.7 to 15.0)	<0.001*
	OSS	11.0 (7.0 to 15.8)	4.5 (0.5 to 10.3)	0.003*
6 weeks	DASH	13.3 (3.5 to 26.7)	2.9 (-5.6 to 12.1)	0.020*
	OSS	6.0 (2.0 to 14.8)	2.0 (-1.0 to 6.5)	0.055

**Table 3-4: Median and inter-quartile ranges for changes in DASH and OSS compared to baseline at 2, 4 and 6 weeks after injection for the steroid and the NSAID groups. \* denotes a statistically significant difference**

Figure 3-7 plots the trend in DASH score for difference between the two treatment groups, with 95% confidence intervals; if confidence interval contains 0, then difference between treatments is not significant. Figure 3-8 plots the same for OSS.



**Figure 3-7: Changes in DASH score (Steroid – Tenoxicam) at 2, 4 and 6 weeks compared to baseline after injection. Patients in the Steroid group show significantly higher scores than the Tenoxicam group at all occasions.**



**Figure 3-8: Changes in OSS (Steroid – Tenoxicam) at 2, 4 and 6 weeks compared to baseline after injection. Patients in the Steroid group show significantly higher scores than the Tenoxicam group at 2 and 4 weeks.**

### 3.3.4 Subjective assessment.

In the Subjective Categorical Assessment (with one patient lost to follow-up in each group) more patients in the steroid group (23 of 26) felt that the injection helped with their pain, compared to the NSAID group (15 of 30) (chi-squared,  $p = 0.005$ ). In all, eight patients in the steroid group decided to take additional oral analgesia during the study period compared with 15 in the NSAID group; this difference was not significant (chi-squared,  $p = 0.235$ ). No patient in either group took supplementary NSAIDs during the study period. Overall, 12 patients in the steroid group felt their shoulder was much better, and eight felt it was slightly better than before the injection. In the NSAID group seven patients reported their shoulder to be much better and eight thought it was slightly better. In the NSAID group 15 patients reported their shoulder condition to be either unchanged or slightly worse than before injection. No adverse events or complications, either locally or systemically, were reported in either group.

### 3.4 Discussion

This is the first study that directly compared a subacromial injection of corticosteroid (methylprednisolone) with a subacromial injection of a NSAID (tenoxicam) in the treatment of subacromial impingement syndrome. NSAIDs and corticosteroids are among the most commonly used treatments for subacromial impingement syndrome, but the most effective treatment option remains to be established. There have been a few high quality RCTs that have directly compared an injection of corticosteroid with NSAIDs administered

orally in the treatment of rotator cuff tendonitis<sup>211,212,272</sup>, but none evaluated NSAIDs as a local preparation.

Adebajo et al<sup>211</sup> conducted a prospective double-blind placebo-controlled study comparing triamcinolone hexacetonide injection with oral diclofenac 50 mg every eight hours. At four weeks both treatments were found to be superior to the placebo in reducing pain, improving active abduction and reducing functional limitation. They reported that the improvement with triamcinolone was significantly superior to diclofenac. Petri et al<sup>272</sup> compared subacromial triamcinolone injection with oral naproxen in a randomized, double-blind, placebo-controlled study of 100 patients who had painful shoulders. They compared outcome using degree of active abduction, pain, limitation of function, and a clinical index that combined equally weighted measures of all of these. They concluded that both triamcinolone and naproxen are superior to placebo in the treatment of the painful shoulder but triamcinolone was superior to naproxen in providing pain relief. A meta-analysis by Arroll et al<sup>216</sup> came to the conclusion that subacromial injections of corticosteroids are effective for improvement for rotator cuff tendonitis up to a 9-month period and are also probably more effective than NSAID medication.

White et al<sup>212</sup> found that there was no difference in the short-term efficacy of oral non-steroidal therapy compared to local corticosteroid injection for treatment of acute rotator cuff tendinitis. They conducted a prospective double-blind randomised trial comparing a subacromial injection of 40 g of

triamcinolone acetonide with oral indomethacin (100 mg/day) in forty patients. They repeated the injection and offered medication refill after 3 weeks, if necessary. They found no significant difference between the steroid and the NSAID group at six weeks with respect to the percentage of patients who improved (60 vs 66%) or the degree of improvement in pain and range of motion. A systematic review conducted by the Cochrane collaboration<sup>201</sup> also concluded that although the available evidence from randomised controlled trials supports the use of subacromial corticosteroid injection for disease of the rotator cuff, the effect may be small and short-lived and no better than NSAIDs. Therefore, the available evidence does not conclusively prove that one treatment is better than the other.

A review of the literature also shows that there is no consensus on the type of corticosteroid or the NSAID that offers the best efficacy with minimal side effects. There is a wide spread across the studies in the type, dosage and duration of treatment of both corticosteroids and NSAIDs used in the management of subacromial impingement syndrome.

The results of our study suggest that a single subacromial injection of 20 mg tenoxicam does not have the same efficacy as methylprednisolone in the treatment of subacromial impingement syndrome, as measured by improvement in pain and function at six weeks. The difference was significant even at two weeks after the injection, and was maintained throughout the

study period. One possible explanation could be that tenoxicam may have a shorter duration of action than methylprednisolone. Although, tenoxicam is a long-acting NSAID with a median half-life of elimination from the body of 72 hours (range 42-100 hours) and its pharmacokinetic properties have been studied after oral, intramuscular or intravenous routes, no data exists for local or periarticular injection<sup>277,301</sup>.

Tenoxicam has been used as a subacromial injection for the treatment of acute rotator cuff tendinitis in a double-blinded placebo controlled trial of 80 patients by Itzkowitch et al<sup>215</sup>. They found that locally administered tenoxicam was effective in alleviating pain and improving shoulder mobility compared to a placebo at four weeks. In that study patients had weekly injections of tenoxicam for up to four weeks (at the investigator's discretion, based on clinical improvement). They noticed only a short duration for observing a clinical effect – within one week, about two third of patients showed improvement. The difference in improvement with the placebo group was already significant at one week and was observed at every visit but they did not make comparisons with any current treatment. In our series, the first evaluation of functional response took place two weeks after injection and may have missed any therapeutic effect of tenoxicam, simply leaving the placebo effect. In order to maintain the double-blinded nature of our study, the protocol was based on our normal practice where patients receive a single subacromial injection of methylprednisolone and have an outpatient follow-up six weeks later.

Yoon et al<sup>302</sup> conducted a RCT to determine if intra-articular injections with a high-dose corticosteroid (triamcinolone acetonide) improves pain and function in patients with adhesive capsulitis better than a low dose and found no significant difference between 20mg and 40mg of corticosteroid suggesting that corticosteroid may not produce a dose-dependent effect. Hence, although tenoxicam was not found to be as effective as corticosteroid for the treatment of subacromial impingement pain, further investigations may be needed to determine the dose, frequency and volume of tenoxicam that will provide the optimum effect with the fewest complications.

Studies have demonstrated postural, kinematic, and muscle changes to directly or indirectly alter the subacromial space dimension and relationships to the structures within the subacromial space leading to subacromial impingement syndrome<sup>303</sup>. These multiple factors are typically present in some combination, as opposed to a single factor like inflammation. The difference in treatment effects for corticosteroid and NSAIDs may be due to their different pharmacological mechanisms. Corticosteroids are potent anti-inflammatory and pain modulating drugs and may act through both local and systemic mechanisms. With pharmacologic actions on virtually every tissue, corticosteroid not only relieves pain but may also exert a positive influence on the patients' mood<sup>273</sup>. NSAIDs, are only likely to be able to reduce inflammation and alleviate pain, with no effect on the general wellbeing of the patient.

Local injections of corticosteroids can have potentially serious side effects. Corticosteroids are known to inhibit collagen synthesis, delay tendon healing and can cause late tendon ruptures<sup>219,269</sup>. They are shown to cause tendon atrophy on histologic studies<sup>220</sup>. Importantly for the surgeon, there is evidence to support that a series of more than three preoperative injections of corticosteroids are associated with decreased suture pull-out strength, weaker rotator cuff repair, and increased rate of failure of the rotator cuff repairs<sup>304,305</sup>. Therefore, Blair et al recommended that, at most, two subacromial injections of corticosteroids be given<sup>267</sup>.

As far as we are aware local injections of NSAIDs have not been associated with clinically significant changes in cartilage or soft tissue. Animal studies where NSAIDs have been administered intra-articularly did not show significant cartilaginous changes<sup>306,307</sup>. A study by Dingle shows that NSAIDs have variable effects on the matrix of human articular cartilage but the oxycam group of NSAIDs appear to have no significant effect on collagen matrix synthesis<sup>308</sup>. Histologic and basic science studies in vitro have shown varying results when evaluating the effects of NSAIDs on tendon histopathology but these results have not been extrapolated to the clinical setting<sup>309,310</sup>.

This study has some limitations. The endpoint in our analysis was at 6 weeks, which is a relatively short observation period compared with the course and treatment for subacromial impingement, which continues for a longer time and patients could have multiple injections during their

treatment. The follow-up in the present study was limited to six weeks and consequently the results do not address long-term outcome or the occurrence of adverse events, although a study by Cummins et al on the temporal outcomes of non-operative treatment for impingement syndrome, suggests that the outcome at six weeks following a subacromial injection can predict the long-term outcome<sup>311</sup>. Moreover, in our study the results were significantly different at two weeks and remained so at four and six weeks. A longer follow-up is highly unlikely to come to a different conclusion.

The diagnosis of subacromial impingement syndrome was made clinically with plain radiographs of the shoulder taken to rule out other causes of shoulder pain. Specifically, advanced imaging modalities like ultrasound or MRI were not used to make the diagnosis of impingement syndrome or to exclude the presence of a rotator cuff tear. This could be considered as a limitation of the study but Gartsman<sup>312</sup> has stated that impingement syndrome is a clinical diagnosis. He described that impingement syndrome may exist in the presence of a clear well defined subacromial space and the diagnosis of subacromial impingement is therefore made on clinical examination<sup>312</sup>. Likewise, only patients with muscle wasting and weakness on clinical examination were considered to have a rotator cuff tear and excluded from the trial. We acknowledge that this may not have identified everyone with a tear especially those with partial thickness tears. Moreover, when injecting the subacromial space, we used immediate improvement in shoulder pain (Neer's injection test<sup>9</sup>) as an indicator of accurate placement. Some studies have shown a high incidence of non-bursal injections of the

shoulder when the injections are administered blind<sup>313,314</sup>. Use of an advanced imaging technology like ultrasound guidance would have been a more accurate method of injection. Other studies have shown that blind injection into the subacromial bursa is as reliable as USG-guided injection and could therefore be used in daily routine<sup>315,316</sup>.

The current study was designed as a pragmatic and not an explanatory trial. Explanatory trials are aimed to find out how and why an intervention works and therefore should be performed under strictly standardized conditions. Pragmatic studies do not assess the efficacy of treatment protocols but assess the question of whether the treatments work in a real-life setting and so, the intervention can be less strictly defined and can be adapted to the clinician's discretion<sup>317</sup>. The other limitation was in excluding patients who were taking regular oral NSAIDs from the trial. Many patients with subacromial impingement may be taking NSAIDs, which would have excluded them from this study, making it difficult to extrapolate the results to all patients seen in clinical practice.

### **3.5 Conclusion**

In our group of patients with subacromial impingement syndrome, a single subacromial corticosteroid injection of 40 mg of methylprednisolone provided a significantly better outcome than a single injection of 20 mg of tenoxicam when shoulder function was assessed at two, four and six weeks. Both methylprednisolone and tenoxicam injected locally are found to be safe and well tolerated. Immediately following the injection, both groups experienced a

significant reduction in shoulder pain indicating accurate placement of the injection in subacromial bursa. Subacromial corticosteroid injection could be used as a short-term therapy in the management of subacromial impingement syndrome.

## Chapter 4 Ultrasound dimensions of the rotator cuff in asymptomatic young healthy adult shoulders

### Summary:

*In this chapter, the use of ultrasonography for diagnosing rotator cuff pathology is explored. This chapter describes an observational study to define the dimensions of the supraspinatus and other rotator cuff tendons in an asymptomatic young adult population using ultrasound and compare it with their contralateral shoulder. The study also looks for correlations with gender, height, weight and hand dominance.*

### Declarations:

*The ultrasonography protocol was written with the help of Dr Santosh Rai (Consultant Musculoskeletal Radiologist). Dr Santosh Rai and Dr Richard Wellings made shoulder assessments. Data collected by the candidate. Statistical advice given by Dr Helen Parsons.*

### This work has been published

*Karthikeyan S, Rai SB, Parsons H, Drew SD, Smith CD, Griffin DR: Ultrasound dimensions of the rotator cuff in young healthy adults. Published in J Shoulder Elbow Surg. 2014 Aug 23(8):1107-1112.*

### This work has been presented

*The normal ultrasound dimensions of the rotator cuff in healthy young adults. British Elbow and Shoulder Society 2012 Torquay 15th June 2012*

## 4.1 Introduction

### 4.1.1 Ultrasound

Ultrasound refers to sound waves with a frequency greater than the upper limit of the human hearing range. The commonly accepted range of human hearing is 20 Hz to 20 kHz, although it varies between individuals based on their age, the general condition of their ear and nervous system<sup>318</sup>. This range narrows during life with the upper frequency limit being reduced as we grow older<sup>319</sup>.

Ultrasound devices are used in various fields and can operate with frequencies ranging from 20 kHz up to several gigahertz (GHz) (Figure 4-1).

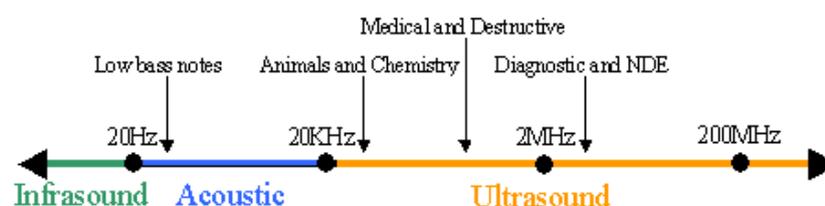


Figure 4-1: Frequencies of sound waves and their applications

In manufacturing and industry, ultrasound allows non-destructive testing of structures and products, where it is used to detect invisible flaws. It can be used to detect objects and measure distances (sonar). In the wild, animals like bats and whales use ultrasound to locate preys and negotiate obstacles. Ultrasound is used for medical imaging, where it is used both in veterinary medicine and human medicine. Ultrasound also has therapeutic applications and has been used by physical and occupational therapists to treat soft tissue conditions like tendonitis, muscle strains and ligament sprains. Focused high power ultrasound

pulses can be used to treat cataracts by phacoemulsification or break calculi like renal and gall stones in a process called lithotripsy.

#### 4.1.2 Ultrasonography

Ultrasonography (USG) or sonography is a diagnostic imaging technique to visualise internal body structures like muscles, tendons, blood vessels and internal organs using ultrasound. Pulses of ultrasound waves are sent from a probe (transducer) into the tissue to be examined. Some of these sound waves are reflected by the tissues, which are captured and displayed as an image. The vast majority of musculoskeletal USG images are produced on a simple grey scale i.e. in a black and white format, where each white dot on the image represents a reflected sound wave. Sound waves are examples of mechanical waves and therefore the denser a material, the more reflective it is and the whiter it appears on the screen. For example, cortical bone is dense and appears white while water which allows sound waves to pass through it and therefore is the least reflective material in the body, appears black on the image<sup>320</sup>. Advanced USG techniques like colour and power Doppler imaging are used in the assessment of vascular tissues and produce colour images based on the degree of blood flow to the tissues.

Musculoskeletal ultrasound has become an established imaging technique for the diagnosis and follow-up of patients with soft tissue pathology over the last two decades<sup>320</sup>. Seltzer first described ultrasound as a promising new method for detecting intra-articular effusions of the shoulder after he used it on six rhesus monkeys<sup>185</sup>. Recent technological advances resulting in faster computers and

higher frequency transducers have made ultrasonography a widely used diagnostic tool. Besides looking at muscles, tendons and ligaments, it can also be used to detect fluid collection and to visualise structures such as cartilage and bone surfaces in a joint<sup>321,322</sup>. Although, USG itself is non-invasive, it can be used for guidance when performing invasive procedures like aspiration, injection or biopsy.

#### 4.1.3 Transducers

Transducers come in different shapes and sizes. A linear probe uses high frequency waves to create high-resolution images of structures near the body surface. This makes it ideal for musculoskeletal and vascular imaging. A curvilinear probe uses lower frequency ultrasound, which penetrates deep and provides a wide depth of field. These probes are used for viewing intra-abdominal structures. Phased array probes produce a large depth of field with a small footprint, allowing visualization of deep structures through a small acoustic window. This makes it ideal for examination of thoracic cavity as ultrasound waves are passed between the ribs.

The size of transducer footprint (area of the transducer in contact with the surface of the skin) is critical for the area to be examined and the examination technique itself. A probe with a smaller footprint may be advantageous when using USG in uneven areas or negotiating convex/concave body surfaces as it provides better contact between the probe and the skin. If the footprint is too small vision can become “tunneled”, whereas a larger footprint can give a wider picture and improved lateral resolution<sup>323</sup>.

When using ultrasound, a compromise had to be found between image

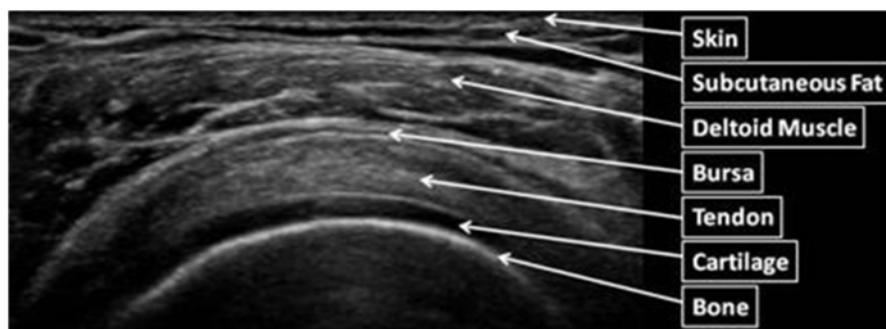
resolution and the depth of penetration of tissues. High frequency transducers (7.5 – 20 MHz) produce better spatial resolution but their depth of penetrance is shallower than a lower frequency transducer (3.5 – 5 MHz). In-plane spatial resolutions of 0.2 – 0.4 mm can be achieved employing transducers with frequencies in the range 9–13 MHz, which is even higher than the spatial resolution of some MR sequences<sup>324</sup>.

Therefore, selection of an appropriate transducer is based on the structures of interest for the study and the type of examination planned. In general, high frequency linear transducers are best to obtain high quality, high-resolution images of superficial structures like tendons and ligaments.

#### **4.1.4 Ultrasonography in shoulder**

Ultrasonography has many advantages, which make it an attractive modality for the evaluation of rotator cuff – it is portable, quicker, relatively inexpensive, uses non-ionising radiation and is non-invasive, all of which contributes to high patient satisfaction. Besides, the “real time” capability of USG allows dynamic assessment of muscle, tendon and joint movements, which may offer an advantage over static examinations like MRI in detecting subtle structural abnormalities. There are no known risks to the patient from ultrasound when properly performed. But, USG is the most operator dependent imaging modality. Therefore, the value of any information obtained by USG is highly dependent on the experience and expertise of the examiner<sup>320</sup>. Operator inexperience can lead to incorrect acquisition and interpretation of images.

For the diagnosis of full-thickness tears alone, Ultrasound has shown to be accurate with high sensitivity and specificity (92-94%) comparable to that of the much more costly and invasive Magnetic Resonance Arthrogram (MRA)<sup>162,184</sup>. Authors of a recent Cochrane review have concluded that MRI, MRA and USG have good diagnostic accuracy and any of these tests could equally be used for detection of full thickness tears in people with shoulder pain for whom surgery is being considered<sup>162</sup>. The same authors have found that both MRI and USG may have poor sensitivity for detecting partial thickness tears, and the sensitivity of USG may be much lower than that of MRI with USG having a sensitivity of only 52% (95% CI 33% to 70%)<sup>162</sup>. Although, other studies have shown higher sensitivities (66-84%) and specificities (89-93.5%), they are still inferior to that of MRA in diagnosing partial-thickness tears<sup>184,187</sup>.



**Figure 4-2: Transverse view of a normal supraspinatus tendon on ultrasound showing the different tissue layers (source: [www.radiopaedia.org](http://www.radiopaedia.org)).**

Several sonographic criteria have been described to correctly diagnose rotator cuff tears by Ultrasound<sup>196,325</sup>. For full-thickness tears these are relatively straightforward and may include non-visualisation of the rotator cuff or a focal tendon defect<sup>196</sup>. For partial-thickness tears, flattening of the bursal surface may indicate a bursal side partial-thickness tear, while a distinct hypoechoic or mixed hyper- and hypoechoic defect at the articular surface may indicate an articular side partial-thickness tear<sup>326</sup>. In 80% of patients with partial thickness tears, an

abnormal hypoechoic area was seen within the supraspinatus tendon<sup>196</sup>. Other authors have described associated secondary signs like greater tuberosity cortical irregularity<sup>196,327,328</sup> or fluid within the subacromial-subdeltoid bursa and joint effusion<sup>196,329,330</sup>, which may be of help in diagnosing difficult cuff tears.

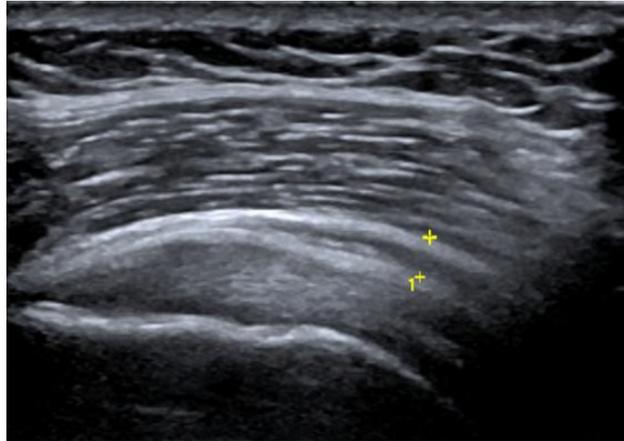


Figure 4-3: USG image showing an enlarged SASD bursa with normal supraspinatus tendon

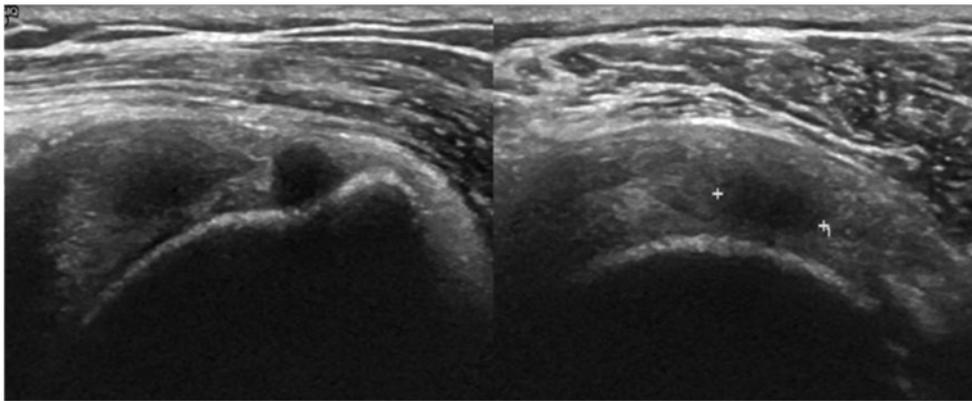


Figure 4-4: USG images (transverse and sagittal) showing an articular sided partial thickness tear of the supraspinatus tendon.

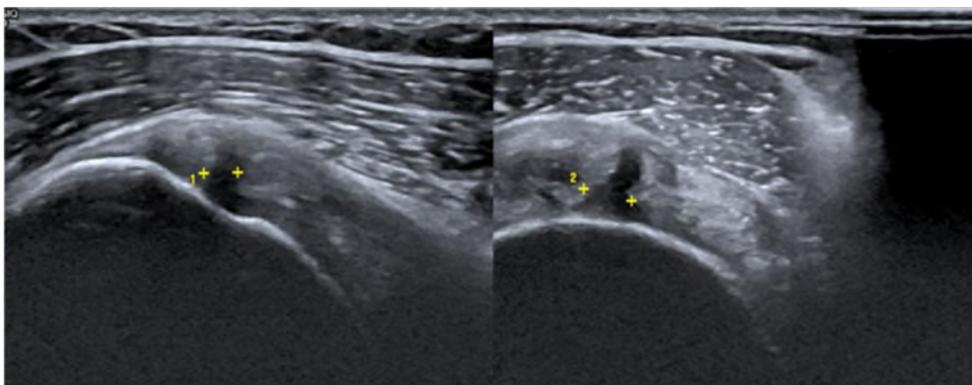


Figure 4-5: USG images (transverse and sagittal) showing a full thickness tear of the supraspinatus tendon

Thinning of the affected tendon is one criteria that is often used to diagnose a rotator cuff tear (full-thickness and partial-thickness) <sup>163,195-197,331,332</sup>. It is based on the assumption that the normal dimensions of the rotator cuff are known and a decrease in tendon thickness can be visualised. Although there is an abundance of literature on the pathological appearances and frequencies of rotator cuff pathology, a detailed review of the literature has revealed no previous studies looking at the cuff dimensions in a young healthy population using ultrasonography. Specifically, we could not find any study that explored any association of the subjects' gender, hand dominance, weight, height or other muscle dimension with their rotator cuff measurements. Defining the parameters for the normal rotator cuff will create a knowledge base and help clinicians to make a comparison between normal and pathological cuff.

I designed an observational study to measure the normal ultrasound dimensions of the rotator cuff.

## **4.2 Study design**

### **4.2.1 Aim**

The aim of this study is to define the dimensions of the supraspinatus and other rotator cuff tendons in a healthy young adult population using ultrasound and to compare it with their contralateral shoulder. Correlations with gender, height, weight, hand dominance and other muscle dimensions will also be explored to see if there is a relationship.

#### **4.2.2 Ethics approval**

The study was reviewed and approved by the Biomedical Research Ethics Committee of Warwick Medical School (Appendix: E).

#### **4.2.3 Recruitment**

Flyers and letters were distributed among the staff and students of Warwick Medical School detailing the study and inviting them to participate (Appendix: F). The first sixty volunteers (thirty males and thirty females) who responded to the invite and who fulfilled the eligibility criteria formed the study population.

#### **4.2.4 Inclusion and Exclusion Criteria**

All healthy adults (over 18 years) under the age of forty years, who had no significant medical conditions and had no shoulder problems, were considered eligible to participate in the study. Anyone with significant co-morbidities or who had undergone previous shoulder surgery was excluded. Volunteers who have or have had pain in their shoulder or who were limited in their daily activities due to shoulder problems in the preceding four weeks were also considered ineligible to participate in the study.

#### **4.2.5 Consent**

Each volunteer who expressed an interest was given a detailed information sheet (Appendix: G) about the study. This provided the background, objective, the benefits and potential risks involved in participating in the study. It was made clear that the study was entirely voluntary and that they are free to withdraw from it at any time without reason or an explanation. They were given opportunities to clarify any doubts they had about the study with the investigators. Once they were completely satisfied and expressed their interest

to proceed with the study, they were asked to sign a consent form (Appendix: H). They then underwent an ultrasound assessment of both shoulders in a private consultation room by a musculoskeletal radiologist.

#### 4.2.6 Methods

Demographic details including age, height, weight, hand dominance, sports activities, co-morbidities, smoking and drinking habits were collected for each individual. As the results of USG are highly dependent on the expertise of the examiner, a single experienced Consultant musculoskeletal radiologist (Dr Santosh Rai, Consultant Radiologist at University Hospitals Coventry and Warwickshire NHS Trust, Coventry) who routinely performs ultrasound assessment of shoulders carried out all the measurements.

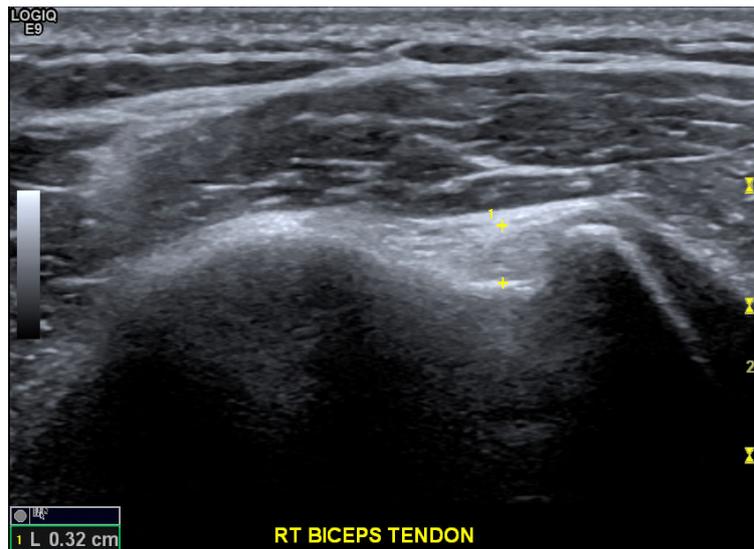
Both shoulders were scanned in each individual sequentially. A GE Logiq E9 (GE Healthcare, Chalfont St.Giles, United Kingdom) ultrasound scanner with a 10 – 15 MHz linear array transducer was used for all assessments. The scan was performed with the subject in the upright (seated) position facing the examiner. The subject could follow the ultrasound assessment on the screen, which enhanced their co-operation for the study. The shoulder and the whole upper limb were exposed allowing free movement at the shoulder joint during the examination. There is an infinite variety of potential ultrasound techniques described in the literature. We used a standardized examination protocol starting with an examination of the acromioclavicular joint and continued with transverse and longitudinal scans of each of the following structures.

The following structures were visualised in sequence and measurements were taken as described for each structure. To minimise bias, all measurements were taken with reference to bony landmarks.

1. Tendon of long head of biceps
2. Subscapularis
3. Supraspinatus
4. Subacromial bursa
5. Infraspinatus
6. Deltoid

#### **4.2.6.1 Biceps tendon**

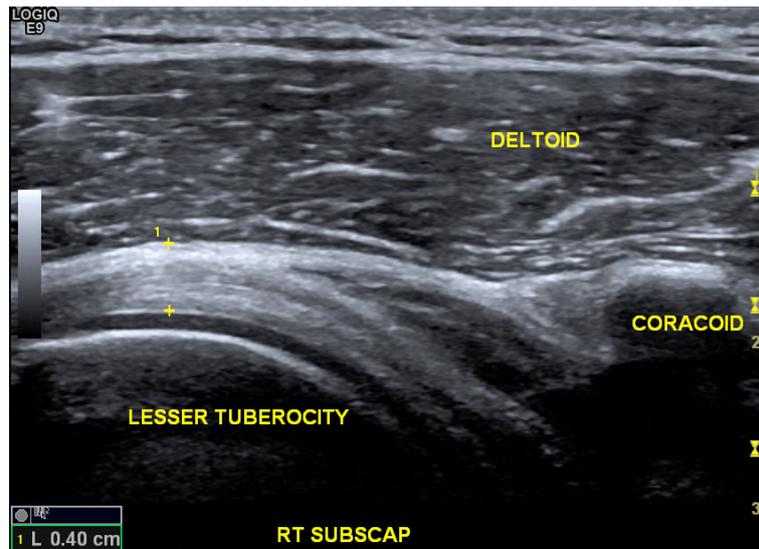
The biceps tendon was examined first with the patient placing their hand on the knee, elbow flexed to 90 degrees and the forearm resting in a supine position on the lap. The tendon of the long head of biceps is visualised in the intertubercular groove under the transverse humeral ligament in both transverse and longitudinal sections. The tendon is followed proximally through the rotator cuff interval towards its attachment on the glenoid tubercle and the superior labrum to rule out any pathology like tendon tears or subluxation. The thickness of biceps tendon was measured at its maximum in the transverse view at the highest point of the groove (Figure 4-6).



**Figure 4-6: Biceps Transverse section**

#### **4.2.6.2 Subscapularis**

To visualise subscapularis, the arm is kept in the same position as above and is externally rotated. This pulls the attachment of the subscapularis tendon allowing the tendon to be traced both longitudinally and transversely. Assessments can be made for tendinopathy or tears of the tendon and subluxation of the biceps tendon at this stage. Dynamic assessment of the tendon integrity can also be made. With the arm in external rotation, the thickness of the subscapularis tendon was measured just medial to its insertion at the lesser tuberosity (Figure 4-7).



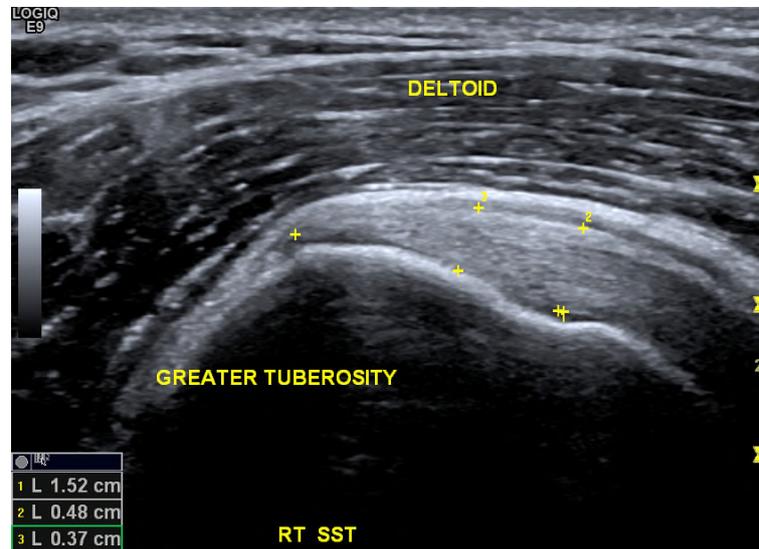
**Figure 4-7: Thickness of subscapularis tendon**

#### **4.2.6.3 Supraspinatus**

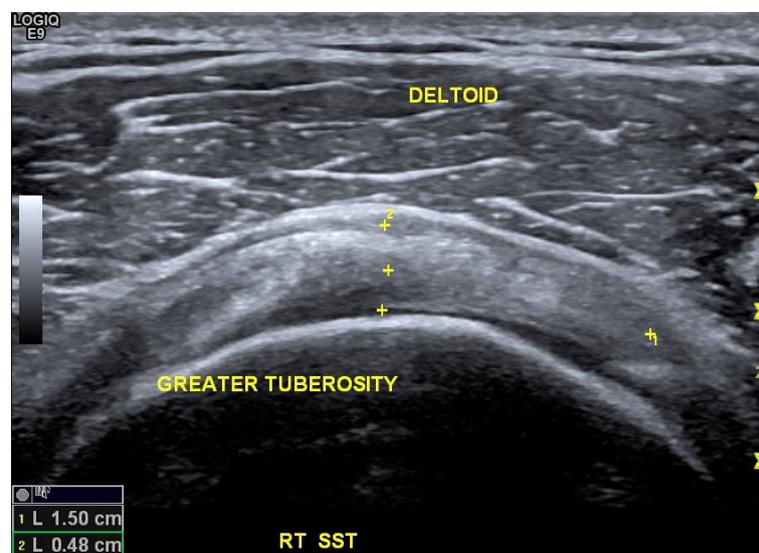
The supraspinatus tendon is best demonstrated with the arm placed behind the back leaving the shoulder in extension and internal rotation, the so called reaching to get wallet from back pocket or scratching between shoulder blade positions. The normal rotator cuff is slightly hyperechoic when compared to the overlying deltoid muscle and assumes a convex curvilinear course when it passes over the humeral head and flattens out as it inserts over the greater tuberosity. The tendon was imaged in both transverse and longitudinal planes with particular emphasis on the distal attachment as most tears occur in this region.

The maximal medio-lateral width of supraspinatus footprint at its insertion was measured in the coronal view of the tendon (Figure 4-8). Two further measurements were made to assess the thickness of supraspinatus tendon in the same view. The first was made at the medial edge of footprint and the second, at

mid-point of the footprint (Figure 4-8). In addition, the thickness of supraspinatus tendon on the sagittal view was done at a fixed-point 15mm posterior to the biceps tendon (Figure 4-9).



**Figure 4-8: Maximum width of footplate (1) and thickness of supraspinatus at the medial edge of footplate (2) and at the middle of footplate (3)**



**Figure 4-9: Thickness of supraspinatus tendon in the sagittal plane**

#### **4.2.6.4 Subacromial subdeltoid (SASD) bursa**

The thickness of the subacromial subdeltoid bursa was measured on the coronal view in the same plane as the thickness of the supraspinatus tendon (Figure 4-10). It is normally seen as a single thin hyperechoic line running parallel to the

supraspinatus tendon superiorly. Any abnormality like thickening of bursa or bursitis when the hyperechoic line is separated by hypoechoic fluid is noted.

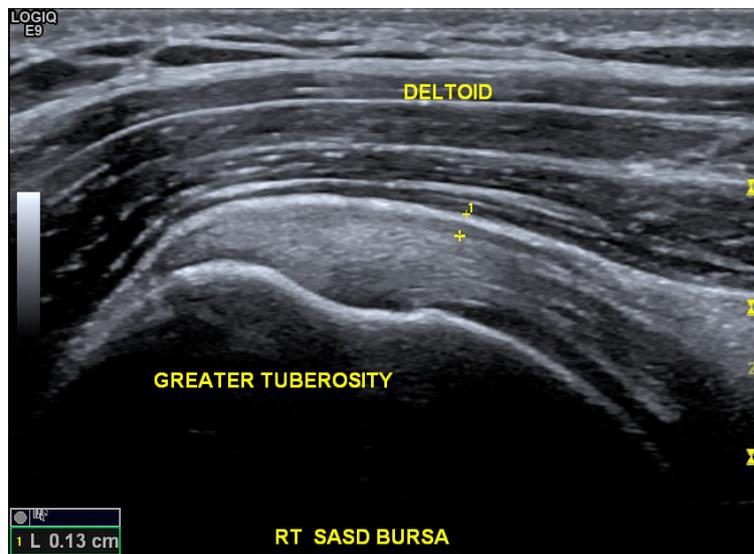


Figure 4-10: SASD Bursa

#### 4.2.6.5 *Infraspinatus and Deltoid*

Infraspinatus is best visualised by asking the subject to reach across and hold their contralateral shoulder with their arms across the chest. Infraspinatus tendon thickness was measured at the level of the posterior border of the acromion (Figure 4-11) and thickness of deltoid muscle was measured at the antero-lateral edge of acromion (Figure 4-12).

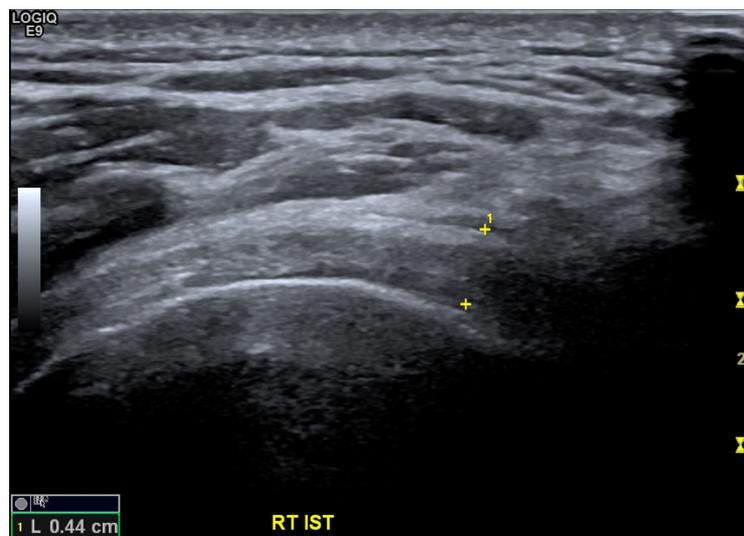


Figure 4-11: Infraspinatus

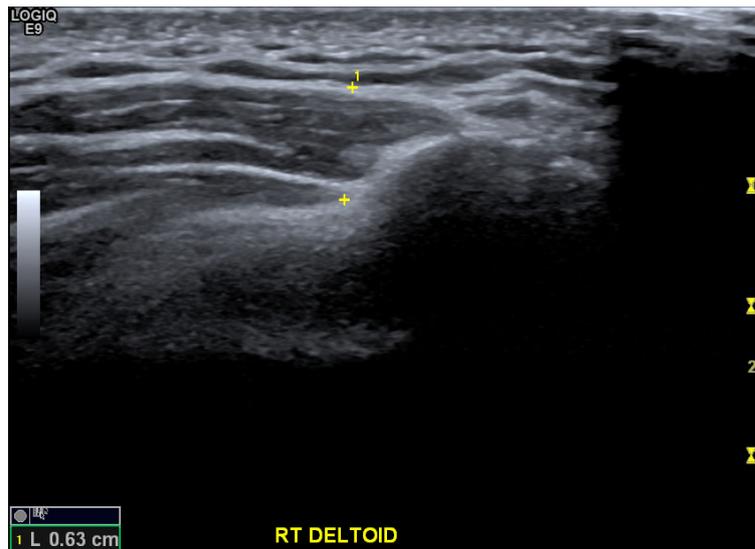


Figure 4-12: Deltoid

#### 4.2.7 Statistical analysis

Differences in measurements between genders and hand dominance were determined by performing t-tests. Due to the low numbers of left-handed participants; arms are classed as “dominant” – the right arm for right-handed participants and the left arm for left-handed participants – or “non-dominant” – the left arm for right-handed participants and the right arm for left-handed participants. For comparisons of arms for each participant (i.e. comparing dominant and non-dominant arms), paired t-tests have been conducted. For comparisons of arms between genders (i.e. comparing dominant arms of men and women) a two-sample t-test was conducted. Pearson’s correlation coefficient was calculated to measure the strength of association between the tendon measurements and the height and weight of the individuals. Differences were considered significant at the 5% level.

##### 4.2.7.1 Correction for multiple testing

Multiple testing refers to the simultaneous testing of more than one hypotheses with a given dataset. The main problem with multiple testing is that, when many

statistical tests are performed, some will return  $p$  values less than 0.05 purely by chance, even if all the null hypotheses are really true. Therefore, with each additional test the probability increases for a researcher to wrongly accept that there is at least one statistically significant result across a set of tests, even when there is no real difference.

Adjustments for making multiple comparisons in large bodies of data are recommended to avoid rejecting the null hypothesis too readily. Although many methods have been described<sup>333,334</sup>, one of the basic and popular fixes to this problem is to apply the Bonferroni correction<sup>335</sup>. This method adjusts the  $p$  value at which a test is considered to show significance based on the total number of tests being performed. The corrected  $p$  value is calculated as the original  $p$  value divided by the number of tests being performed.

By changing the  $p$  value needed to reject the null hypothesis, the Bonferroni correction reduces the number of instances where the null hypothesis appears to be rejected. Although this reduces the number of false rejections, it also increases the number of instances where the null hypothesis is not rejected when in fact it should have been. Bonferroni correction directly targets the Type 1 error problem, but it does so at the expense of Type 2 error.

Technological advances have made it easier to generate large datasets for exploratory analysis, leading to large numbers of hypotheses being tested with no prior basis for expecting many of the hypotheses to be true. In this scenario, high false positive rates are expected unless multiple comparisons adjustments

are made<sup>336</sup>. But, it has been argued that use of multiple testing corrections is an inefficient way to perform empirical research, as they control false positives at the potential expense of many more false negatives<sup>337</sup>.

Therefore, in different branches of science, multiple testing is handled in different ways<sup>337</sup>. Bender and Lange<sup>338</sup> are of the view that such a rigorous assessment is strictly required only in confirmatory studies. A study is considered as confirmatory if the goal of the trial is the definitive proof of a predefined key hypothesis for final decision making. On the other hand, in exploratory studies such as ours, in which data are collected with an objective but not with a pre-specified key hypothesis, multiple test adjustments are not strictly required. They recommend that data of exploratory studies be analyzed without multiplicity adjustment. The present study was an exploratory one and corrections for multiple testing were not applied.

#### **4.2.7.2 Inter and Intra-observer agreement**

Results of USG examination are known to be operator dependent. Therefore, to ensure that the measurements are reproducible, repeat measurements were taken in a random subset of participants (5 men and 5 women, Total-10), both by the initial observer (4 weeks after first measurement) and a second observer who was also an experienced Consultant musculo-skeletal radiologist (Dr Richard Wellings, Consultant Radiologist, University Hospitals Coventry and Warwickshire NHS Trust). From these measurements, Bland-Altman plots were constructed to measure intra and inter-observer agreement.

#### 4.2.7.3 Bland-Altman plots

The Bland-Altman plot is a graphical method to compare two measurements technique. The Bland-Altman plot may also be used to assess the repeatability of a method by comparing repeated measurements using one single method on a series of subjects or to compare measurements by two observers. In this graphical method, the differences between the two techniques are plotted against the averages of the two techniques. Horizontal lines are drawn at the mean difference, and at the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences. It is expected that the 95% limits include 95% of differences between the two measurements or measurement methods. The original Bland-Altman publication has been cited on more than 11,500 occasions-compelling evidence of its importance in medical research<sup>339</sup>.

### 4.3 Results

A total of one hundred and twenty shoulders from sixty participants (thirty male and thirty female) were scanned. Fifty-five participants were right hand dominant and five participants were left hand dominant. Participants' age, height, weight and hand dominance are shown in [Table 4-1](#).

PARTICIPANT CHARACTERISTICS		FEMALES (n=30)	MALES (n=30)
Mean age in years (range)		26.7 (21 - 39)	29.9 (23 - 39)
Mean height in metres (range)		1.63 (1.50 - 1.78)	1.80 (1.70 - 1.95)
Mean weight in kilograms (range)		60.6 (45 - 77)	81.4 (67 - 100)
Mean BMI in kg/m <sup>2</sup> (range)		24.96 (17 - 31)	22.73 (22 - 33)
Hand dominance (n)	Right handed	28	27
	Left handed	2	3

**Table 4-1: Study participant characteristics by gender**

Both male and female participants were similar in age. Males were taller and heavier than females, but their BMI were similar. Very few individuals in either group were left hand dominant.

#### **4.3.1 Rotator Cuff Measurements**

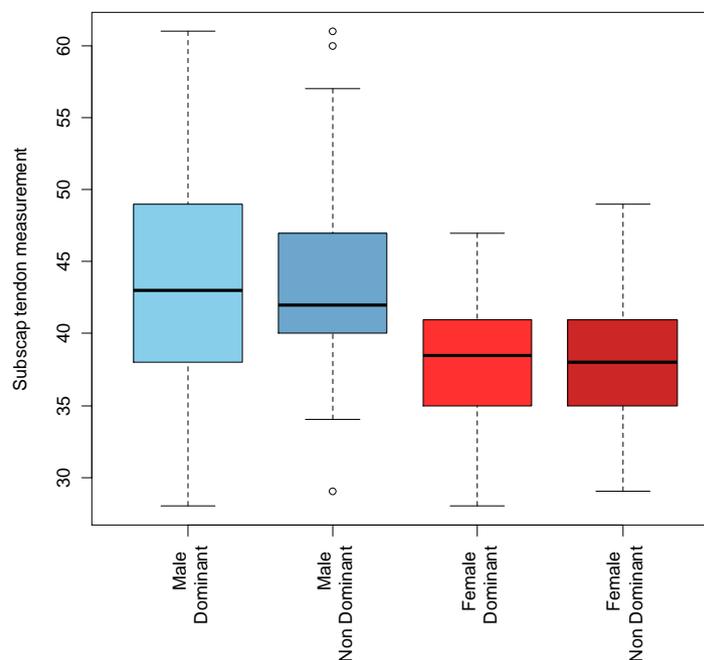
The mean maximum medio-lateral width of supraspinatus insertion onto the humerus in the coronal plane (footprint) was 14.9 mm in males and 13.5 mm in females (Table 4-2). The mean thickness of the supraspinatus tendon varied from 4.9 mm in females to 5.6 mm in males at the medial edge of its insertion and between 3.6 to 4.2 mm at the mid-point of its insertion. Table 4-2 presents the mean  $\pm$  standard deviation (sd) and range for each muscle measurement, separately for male and female participants by hand dominance. All measurements are in millimetres.

VARIABLE	FEMALE (n=30)		MALE (n=30)	
	Dominant Arm	Non-dominant Arm	Dominant Arm	Non-dominant Arm
Subscapularis	3.80± 0.46 (2.8 – 4.7)	3.84 ± 0.5 (2.9 -4.9)	4.40± 0.77 (2.8 – 6.1)	4.39 ±0.74 (2.9 – 6.1)
Supraspinatus Coronal view-Medial edge of FP	5.02 ± 0.59 (3.9 – 6.4)	4.75 ± 0.71 (3.3 – 6.3)	5.77 ± 0.89 (4.6 – 8.2)	5.32 ± 0.82 (4.2 – 7.6)
Supraspinatus Coronal view-Middle of FP	3.74 ± 0.53 (2.6 – 4.8)	3.47 ± 0.5 (2.4 – 4.4)	4.31 ± 0.72 (3.1 – 6.0)	4.0 ± 0.78 (2.7 - 6.4)
Supraspinatus Coronal view-Max width of FP	13.43 ± 1.22 (11.3 – 16.6)	13.52 ± 1.25 (11.6 – 15.4)	14.91 ± 1.54 (12.1 – 18.8)	14.88 ± 1.51 (11.5 – 18.3)
Supraspinatus sagittal view	4.74 ± 0.59 (3.6 – 6.1)	4.47 ± 0.57 (3.7 – 5.9)	5.2 ± 1.03 (3.8 – 8.1)	4.99 ± 0.88 (3.8 – 7.0)
Infraspinatus	4.4 ± 0.44 (3.6-5.2)	4.32 ± 0.49 (3.5-5.5)	4.85 ± 0.63 (3.8-6.2)	4.93 ± 0.73 (3.4-6.4)
Biceps tendon	2.94 ± 0.38 (2.2 – 3.9)	2.89 ± 0.37 (2.3 – 4.2)	3.43 ± 0.42 (2.6 – 4.2)	3.27 ± 0.58 (2.2 – 4.6)
Deltoid muscle	6.05 ± 0.79 (4.6 – 8.0)	5.92 ± 0.86 (4.8 – 8.8)	7.12 ± 0.81 (5.4 – 8.8)	7.09 ± 0.97 (5.4 – 9.8)
SASD bursa	1.00 ± 0.22 (6 – 1.5)	0.88 ± 0.18 (6 – 1.3)	1.18 ± 0.26 (8 -1.7)	1.14 ± 0.28 (7 – 1.8)

**Table 4-2: Descriptive statistics for the average (mean ± sd) measurements for both male and female participants in the study. The range for each measurement is shown in parentheses. All measurements are in millimetres. FP-Footprint; SASD-Subacromial subdeltoid**

#### 4.3.1.1 Subscapularis tendon

Boxplots of the measurements for the subscapularis tendon in males and females are shown below in Figure 4-13. Here it can be seen that on average, the male subscapularis tendon is longer than the female for both dominant and non-dominant arms. It can also be seen that for both male and female measurements, the dominant and non-dominant arms have similar mean lengths.



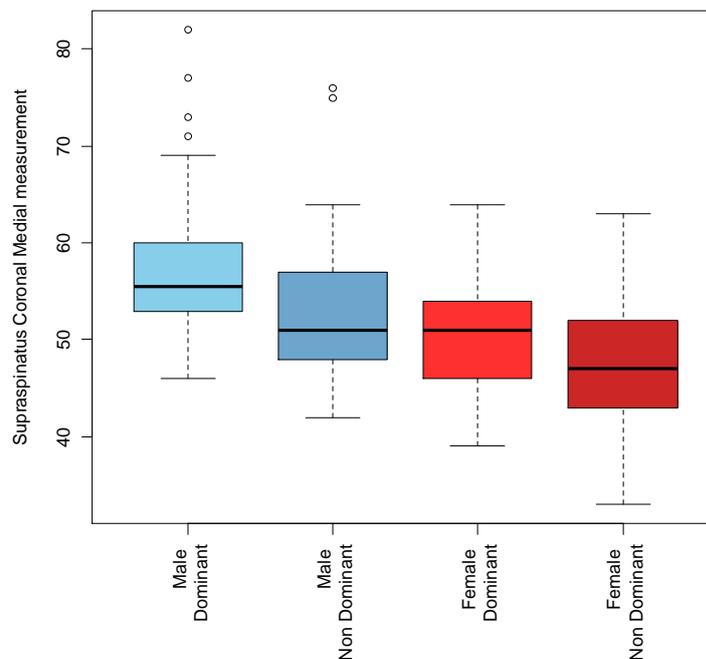
**Figure 4-13: Boxplots of measurements for thickness of subscapularis tendon. Bold line represents the median; box represents the interquartile range (IQR) and the whiskers represent 1.5 times the IQR**

Table 4-3 below shows that the t-tests show a significant difference only for the inter-gender dominant and non-dominant arms. There was no significant difference between the dominant and the non-dominant arms with in the same gender.

Comparison	Average Difference	p value	Measured values
Male: dominant v non-dominant arm	0.007	0.9428	4.40 vs 4.39
Female: dominant v non-dominant arm	-0.043	0.5904	3.80 vs 3.84
Dominant arm: male v female	0.60	0.0006*	4.40 vs 3.80
Non-dominant arm: male v female	0.55	0.0014*	4.39 vs 3.84

**Table 4-3: t-test results for the differences in supraspinatus tendon thickness measurements. Differences are reported as the mean of the first variable minus the mean of the second variable for non-paired tests and mean of the differences for paired tests. \*denotes significance**

#### 4.3.1.2 Supraspinatus at medial edge of footprint



**Figure 4-14: Boxplots of measurements for supraspinatus tendon thickness at the medial edge of the footprint on coronal view. Bold line represents the median; box represents the interquartile range (IQR) and the whiskers represent 1.5 times the IQR**

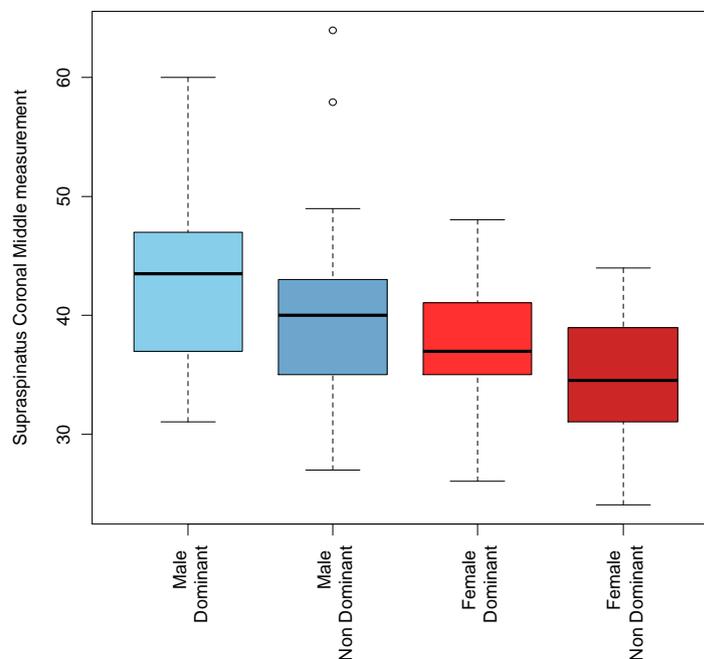
Figure 4-14 shows the boxplots of the measurements for thickness of the supraspinatus tendon at the medial edge of the footprint on the coronal view. It can be seen that on average, the muscle thickness on the male dominant arm is

the largest measurement. Table 4-4 below shows that the differences between the dominant and non-dominant arms of both male and female participants are statistically significant. It also shows that the inter-gender variations for both dominant and non-dominant arms are also statistically significant, although the differences are very small.

Comparison	Average difference	p value	Measured values
Male: dominant v non-dominant arm	0.45	0.0026*	5.77 vs 5.32
Female: dominant v non-dominant arm	0.27	0.0050*	5.02 vs 4.75
Dominant arm: male v female	0.75	0.0004*	5.77 vs 5.02
Non-dominant arm: male v female	0.57	0.0053*	5.32 vs 4.75

**Table 4-4: t-test results for the differences in measurements of supraspinatus tendon thickness at medial edge of the footprint. Differences are reported as the mean of the first variable minus the mean of the second variable for non-paired tests and mean of the differences for paired tests. \*denotes significance**

#### 4.3.1.3 Supraspinatus tendon at middle of the footprint



**Figure 4-15: Boxplots of the measurements of the supraspinatus tendon measurements at the middle of the footprint. Bold line represents the median; box represents the interquartile range (IQR) and the whiskers represent 1.5 times the IQR**

Figure 4-15 shows the boxplots of the measurements for thickness of the supraspinatus tendon at the middle of the footprint on the coronal view, similar to the measurements above (Section 4.3.1.2), on average the muscle on the male dominant arm is the longest measurement and that the muscle measurement is smaller in women as opposed to men.

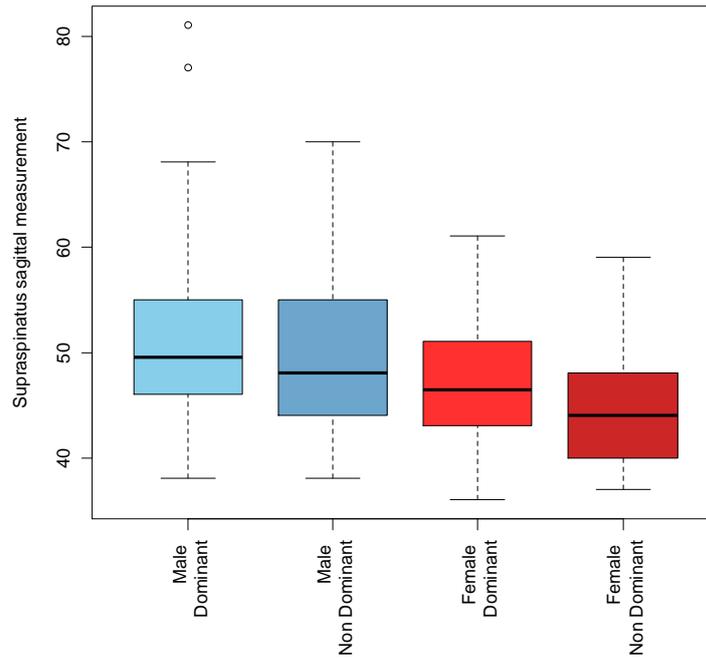
As before, Table 4-5 below shows that the differences between the dominant and non-dominant arms of both male and female participants are statistically significant. It also shows that the variations for both dominant and non-dominant arms between the two sexes are also statistically significant, although the differences are very small.

Comparison	Average difference	p value	Measured values
Male: dominant v non-dominant arm	0.31	0.0220*	4.31 vs 4.0
Female: dominant v non-dominant arm	0.27	0.0073*	3.74 vs 3.47
Dominant arm: male v female	0.57	0.0011*	4.31 vs 3.74
Non-dominant arm: male v female	0.53	0.0031*	4.0 vs 3.47

**Table 4-5: t-test results for the differences in supraspinatus tendon measurements at the middle of the footprint. Differences are reported as the mean of the first variable minus the mean of the second variable for non-paired tests and mean of the differences for paired tests. \*denotes significance**

#### 4.3.1.4 Supraspinatus tendon on sagittal view

Figure 4-16 shows the boxplots of the measurements for the thickness of supraspinatus tendon on sagittal view, where on average the tendon thickness has no differences between arms in men, but is smallest in the non-dominant arm in women. Table 4-6 shows that all these differences are statistically significant except for the difference between the dominant and the non-dominant arms in men. However, all these differences were very small.



**Figure 4-16: Boxplots of the measurements for supraspinatus thickness on sagittal view. Bold line represents the median; box represents the interquartile range (IQR) and the whiskers represent 1.5 times the IQR**

Comparison	Average difference	p value	Measured values
Male: dominant v non-dominant arm	0.21	0.1295	5.20 vs 4.99
Female: dominant v non-dominant arm	0.26	0.0069*	4.74 vs 4.47
Dominant arm: male v female	0.46	0.0388*	5.20 vs 4.74
Non-dominant arm: male v female	0.52	0.0093*	4.99 vs 4.47

**Table 4-6: t-test results for the differences in supraspinatus thickness measurements on sagittal view. Differences are reported as the mean of the first variable minus the mean of the second variable for non-paired tests and mean of the differences for paired tests. \*denotes significance**

#### 4.3.1.5 Supraspinatus Footplate Maximum dimension

Figure 4-17 shows the boxplots for measurements of the maximum dimension of the footplate on sagittal view. Here, it can be seen that the measurements within each gender are approximately similar, but the female measurements are, on average, shorter than the male. Table 4-7 confirms that the inter-gender differences are not statistically significant, but the intra-gender differences are.

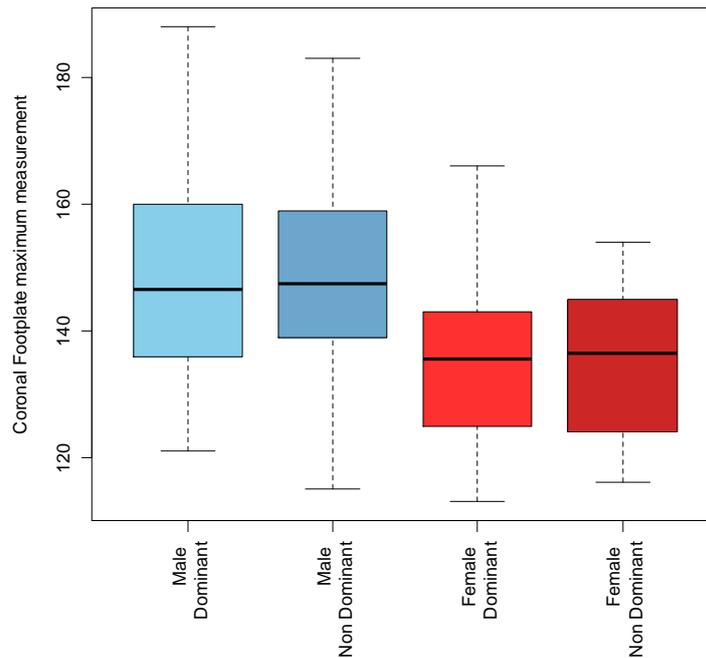


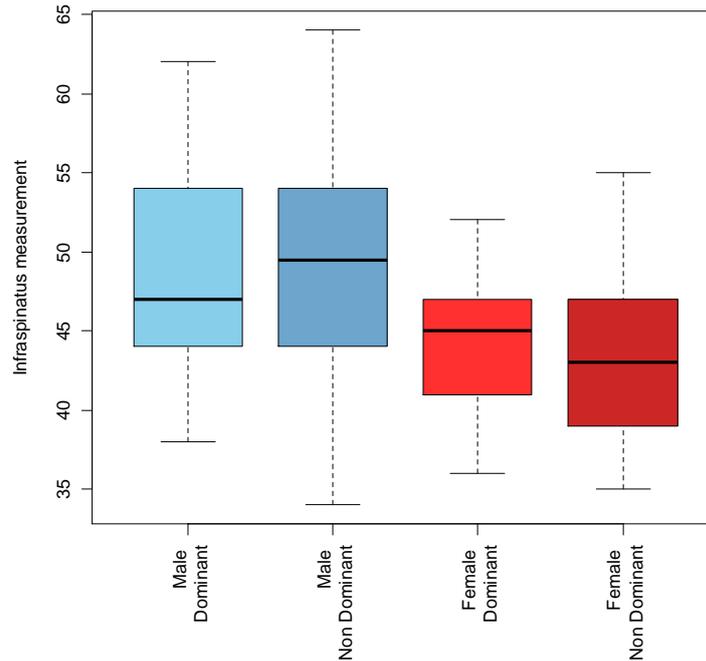
Figure 4-17: Boxplots of measurements for the maximum footplate dimension of the supraspinatus. Bold line represents the median; box represents the interquartile range (IQR) and the whiskers represent 1.5 times the IQR

Comparison	Average difference	p value	Measured values
Male: dominant v non-dominant arm	0.03	0.8668	14.91 vs 14.88
Female: dominant v non-dominant arm	-0.09	0.6067	13.43 vs 13.52
Dominant arm: male v female	1.48	0.0001*	14.91 vs 13.43
Non-dominant arm: male v female	1.36	0.0004*	14.88 vs 13.52

Table 4-7: t-test results for the differences in maximum footplate dimension measurements. Differences are reported as the mean of the first variable minus the mean of the second variable for non-paired tests and mean of the differences for paired tests. \*denotes significance

#### 4.3.1.6 Infraspinus

Boxplots of the infraspinus measurements are shown in Figure 4-18 below. Here, it can be seen that the measurements within both male and female participants are similar, but the measurements in the female participants are generally shorter than the male measurements. T-tests (see Table 4-8) show that the differences, which are statistically significant, are between men and women for both dominant and non-dominant arms.



**Figure 4-18: Boxplots of the infraspinatus measurement. Bold line represents the median; box represents the interquartile range (IQR) and the whiskers represent 1.5 times the IQR**

Comparison	Average difference	p value	Measured values
Male: dominant v non-dominant arm	-0.09	0.4356	4.85 vs 4.93
Female: dominant v non-dominant arm	0.09	0.3794	4.40 vs 4.32
Dominant arm: male v female	0.44	0.0024*	4.85 vs 4.40
Non-dominant arm: male v female	0.61	0.0004*	4.93 vs 4.32

**Table 4-8: t-test results for differences in infraspinatus measurements. Differences are reported as the mean of the first variable minus the mean of the second variable for non-paired tests and mean of the differences for paired tests. \*denotes significance**

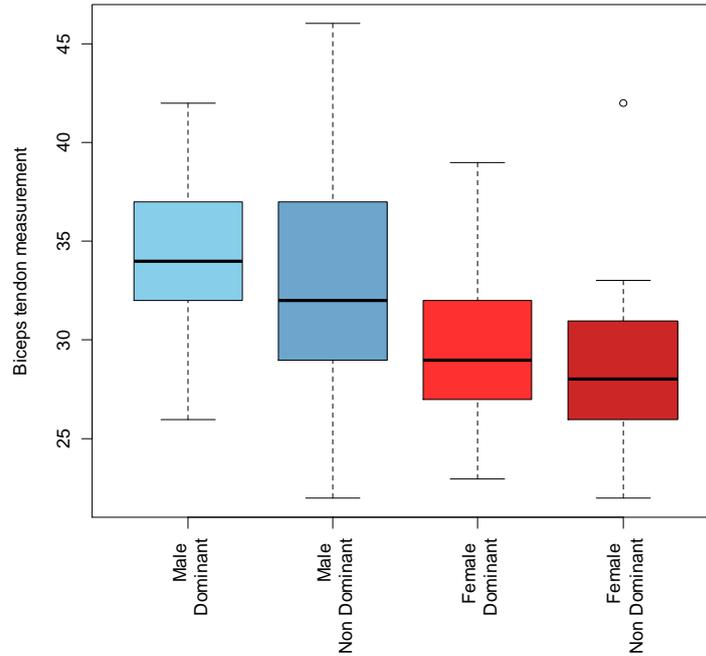
### 4.3.2 Other measurements

Two other muscle measurements outside the rotator cuff were also taken from all participants, which are detailed below. These are of biceps and deltoid.

#### 4.3.2.1 Biceps tendon

Boxplots of the biceps tendon measurements are shown in Figure 4-19 below. Here, it can be seen that the measurements within both genders are broadly

similar and the female measurements are, on average, shorter than the male. Table 4-9 below shows that only the difference between the dominant and non-dominant arms in females is not significantly different, although the differences are very small.



**Figure 4-19: Boxplots of the biceps tendon measurement. Bold line represents the median; box represents the interquartile range (IQR) and the whiskers represent 1.5 times the IQR**

Comparison	Average difference	p value	Measured values
Male: dominant v non-dominant arm	0.16	0.0234*	3.43 vs 3.27
Female: dominant v non-dominant arm	0.05	0.3693	2.94 vs 2.89
Dominant arm: male v female	0.49	0.0001*	3.43 vs 2.94
Non-dominant arm: male v female	0.38	0.0042*	3.27 vs 2.89

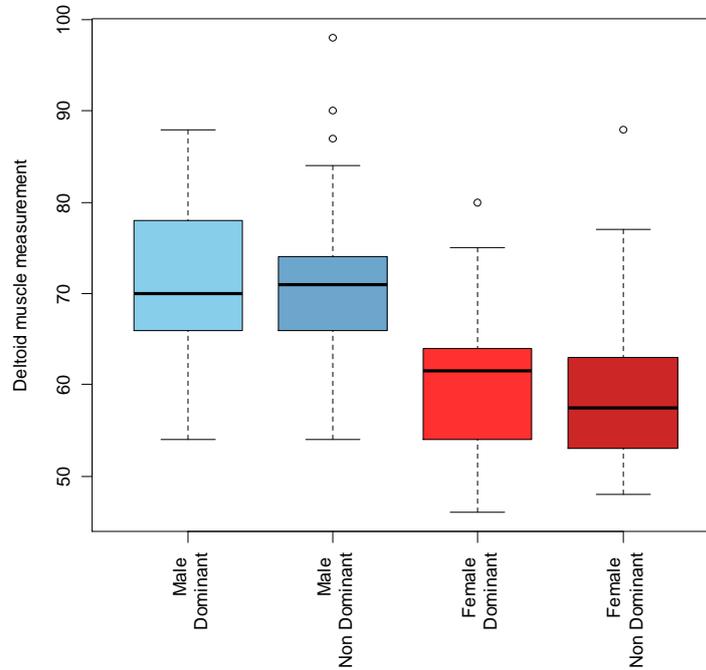
**Table 4-9: t-test results for differences in biceps tendon measurements. Differences are reported as the mean of the first variable minus the mean of the second variable for non-paired tests and mean of the differences for paired tests. \*denotes significance**

#### 4.3.2.2 Deltoid muscle

Boxplots of the deltoid muscle measurements are shown in Figure 4-20 below.

Here it can be seen that the measurements within both genders are broadly

similar and the female measurements are, on average, shorter than the male. Again, t-tests (Table 4-10) confirm that only the intra-gender comparisons are significantly different.



**Figure 4-20: Boxplots of the deltoid muscle measurements. Bold line represents the median; box represents the interquartile range (IQR) and the whiskers represent 1.5 times the IQR**

Comparison	Average difference	<i>p</i> value	Measured values
Male: dominant v non-dominant arm	0.03	0.8560	7.12 vs 7.09
Female: dominant v non-dominant arm	0.13	0.2909	6.05 vs 5.92
Dominant arm: male v female	1.07	$3.152 \times 10^{-6*}$	7.12 vs 6.05
Non-dominant arm: male v female	1.18	$6.318 \times 10^{-6*}$	7.09 vs 5.92

**Table 4-10: t-test results for the differences in deltoid muscle measurements. Differences are reported as the mean of the first variable minus the mean of the second variable for non-paired tests and mean of the differences for paired tests. \*denotes significance**

The measurements for the supraspinatus footprint on the transverse view were significantly different between men and women for both dominant and non-dominant shoulders. The footprint for the dominant arm was measured at 13.43

mm in females compared to 14.91mm in males ( $p < 0.001$ ; t-test). For the non-dominant arm females had a footprint dimension of 13.52 mm compared to 14.88mm in males ( $p < 0.001$ ; t-test). However, the difference between dominant and non-dominant arm among men and women were not found to be significant. The mean difference in supraspinatus footprint dimensions between the dominant and non-dominant arms in men was 0.03 mm ( $p = 0.867$ ; paired t-test) while in women it was 0.09 mm ( $p = 0.607$ ; paired t-test).

The only significant difference between the dominant and non-dominant arms of either sex was found in the thickness of supraspinatus tendon. The difference in thickness was 0.45 mm ( $p = 0.003$ ; paired t-test) in men and 0.27mm ( $p = 0.005$ ; paired t-test) in women at the medial edge of the footprint while at the middle of the footprint it was noted to be 0.31mm ( $p = 0.022$ ; paired t-test) in men and 0.27mm ( $p = 0.007$ ; paired t-test) in women. For all other tendon measurements, a significant difference was found between men and women for both dominant and non-dominant sides but no significant difference between the dominant and non-dominant sides among the same sex. (Table 4-2).

### **4.3.3 Correlation**

#### **4.3.3.1 Rotator cuff measurements**

In this section, the correlation between participant height and weight against the rotator cuff measurements are explored. The Pearson's correlation coefficient ( $r$ ) measures the strength and direction of a linear relationship between two continuous variables. Its value can range from -1 for a perfect negative linear relationship to +1 for a perfect positive linear relationship. A value of 0 (zero)

indicates no relationship between two variables. The strength of the correlation is determined by the magnitude of the Pearson correlation coefficient. There is no consensus for assigning strength of association to particular values, although some general guidelines are provided by Cohen<sup>340</sup> (Table 4-11). A correlation coefficient ( $r$ ) between 0.1 to 0.3 signifies a small correlation between the variables, while a coefficient between 0.3 to 0.5 signifies moderate correlation. Any  $r$  value above 0.5 implies a strong or large correlation between the two variables.

Coefficient Value	Strength of Association
$0.1 <  r  < .3$	small correlation
$0.3 <  r  < .5$	medium/moderate correlation
$ r  > .5$	large/strong correlation

**Table 4-11: Strength of association for Pearson correlation coefficient**

#### **4.3.3.2 Correlation with height**

Relationships between an individual's height and their rotator cuff muscle dimensions were explored to see if the subject's height correlates with their individual muscle thickness. As detailed in Table 4-12 below, none of the measurements showed any strong correlation with height. The supraspinatus footprint dimension in women (both dominant and non-dominant arms) and the supraspinatus thickness on sagittal view in the non-dominant arms of men showed moderate correlation and these were the only values where the correlation was found to be statistically significant. The rest of the

measurements did not show any significant correlation with height, which suggests that height may not be a major factor in predicting muscle length.

Variable	Male		Female	
	<i>Dominant</i>	<i>Non-dominant</i>	<i>Dominant</i>	<i>Non-dominant</i>
<b>Subscapularis tendon</b> Pearson correlation coefficient <i>p</i> value	-0.2834 0.1291	-0.1743 0.3568	0.0843 0.658	0.1471 0.438
<b>Supraspinatus at medial edge of footprint</b> Pearson correlation coefficient <i>p</i> value	-0.249 0.1845	-0.3274 0.0774	0.243 0.1956	0.2228 0.2366
<b>Supraspinatus at middle of footprint</b> Pearson correlation coefficient <i>p</i> value	-0.147 0.4383	-0.2682 0.1519	0.1192 0.5304	0.1639 0.3869
<b>Supraspinatus footprint maximum width</b> Pearson correlation coefficient <i>p</i> value	-0.0204 0.915	0.1804 0.3401	0.4773 0.0077*	0.3712 0.0434*
<b>Supraspinatus on sagittal view</b> Pearson correlation coefficient <i>p</i> value	-0.2441 0.1935	-0.3716 0.0432*	-0.0819 0.6669	-0.0199 0.9171
<b>Infraspinatus</b> Pearson correlation coefficient <i>p</i> value	-0.1301 0.4932	-0.1384 0.4658	0.1667 0.3787	0.0507 0.7903

**Table 4-12: Correlations of the rotator cuff measurements with height. \* indicates a significant correlation at the 5% level.**

#### 4.3.3.3 Correlation with weight

As in the previous section, relationships were explored between an individual's weight and the rotator cuff muscle dimensions to see if the subject's weight correlates with their individual muscle thickness. As Table 4-13 shows none of the muscle dimensions showed moderate or strong correlation with weight and none of the values reached the significance level. Therefore it is unlikely that the

weight of the individual can be used to predict an individual's rotator cuff muscle measurements.

Variable	Male		Female	
	<i>Dominant</i>	<i>Non-dominant</i>	<i>Dominant</i>	<i>Non-dominant</i>
<b>Subscapularis tendon</b> Pearson correlation coefficient <i>p</i> value	0.0328 0.864	-0.0791 0.678	0.2602 0.165	0.0984 0.605
<b>Supraspinatus at medial edge of footprint</b> Pearson correlation coefficient <i>p</i> value	-0.0565 0.767	0.0672 0.724	-0.0170 0.929	0.1706 0.368
<b>Supraspinatus at middle of footprint</b> Pearson correlation coefficient <i>p</i> value	0.0736 0.699	0.2007 0.288	0.0560 0.769	0.2076 0.271
<b>Supraspinatus footprint maximum width</b> Pearson correlation coefficient <i>p</i> value	0.0985 0.605	0.1615 0.394	-0.0366 0.605	0.1747 0.356
<b>Supraspinatus on sagittal view</b> Pearson correlation coefficient <i>p</i> value	-0.0781 0.682	-0.037 0.846	-0.2090 0.268	0.0811 0.670
<b>Infraspinatus</b> Pearson correlation coefficient <i>p</i> value	0.2996 0.108	0.2119 0.261	0.1986 0.293	0.0660 0.729

**Table 4-13: Correlations of the rotator cuff measurements with weight. \* indicates a significant correlation at the 5% level.**

#### **4.3.3.4 Correlation with deltoid and biceps**

Next, the relationship between an individual's physique and the rotator cuff musculature was explored. The measurements for the Biceps tendon and Deltoid muscle were taken from each participant as a proxy measure for their physique.

For the rotator cuff the maximum width of the footprint was taken as a

representative example. As Table 4-14 shows, only the thickness of biceps tendon in the dominant arms of males showed a moderate correlation with the supraspinatus footprint measurement, while the other measurements failed to reach the significance level.

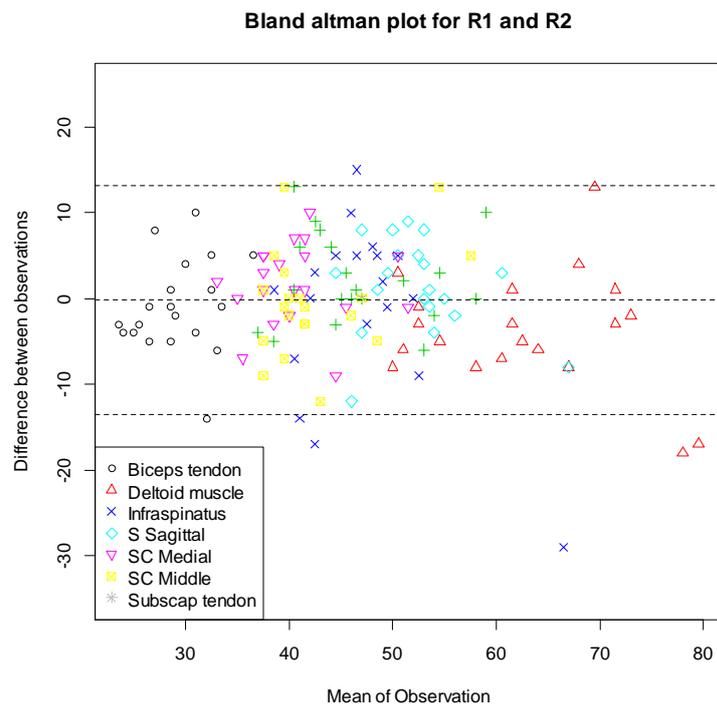
Comparison	Gender	Arm	Correlation	P value
<b>Deltoid and Supraspinatus footprint maximum</b>	Female	Dominant	-0.0831	0.6625
		Non-dominant	0.2179	0.2056
	Male	Dominant	0.0830	0.663
		Non-dominant	0.2116	0.2617
<b>Biceps and Supraspinatus footprint maximum</b>	Female	Dominant	-0.0416	0.8273
		Non-dominant	0.1535	0.4179
	Male	Dominant	0.4812	0.0065*
		Non-dominant	0.0860	0.6413

**Table 4-14: Correlation of supraspinatus footprint with deltoid and biceps thickness.**  
\* indicates a significant correlation at the 5% level.

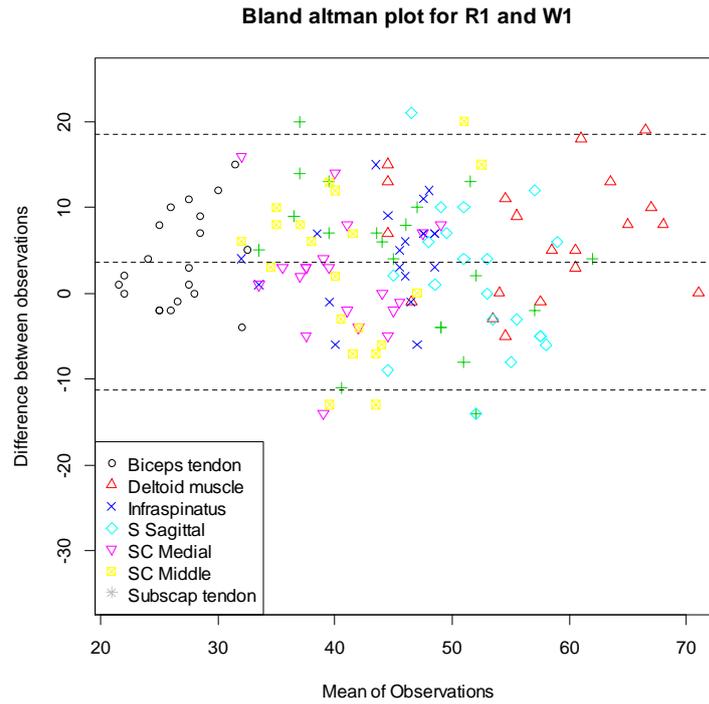
#### 4.3.3.5 Bland-Altman plots

Bland-Altman plots<sup>339,341</sup> were constructed for measuring the intra-observer (Figure 4-21) and inter-observer (Figure 4-22) agreement. The first observer (Dr Rai) repeated all the measurements in a random subset of 10 individuals (5 men and 5 women), four weeks after the first measurement. These two sets of measurements (R1 and R2) were used to calculate the intra-observer variation. A second observer (Dr Wellings) measured the muscle dimensions in the same subset of 10 patients independently using the same protocol. These

measurements were then compared with the original measurements made by Dr Rai to calculate the intra-observer variation. Agreement was analysed by plotting the differences in the two sets of measurements (R1 and W1) against the mean values of these measurements.



**Figure 4-21: Bland-Altman plot for intra-observer agreement; the dashed lines show 95% confidence intervals around the hypothesis of no difference between observations**



**Figure 4-22: Bland-Altman plot for inter-observer agreement; the dashed lines show 95% confidence intervals around the hypothesis of no difference between observations**

The Bland-Altman plots are consistent with the hypothesis that 95% of the differences between the assessments were within  $\pm 1.96$  standard deviations of the mean of the differences (“limits of agreement”), denoting good agreement between the two sets of measurements<sup>339,341</sup> for both inter and intra-observer variations.

#### 4.4 Discussion

Normal anatomy of supraspinatus has been studied extensively in cadavers<sup>15,342-345</sup>. Itoi et al<sup>345</sup> studied morphology of the rotator cuff in 41 cadaveric shoulders and measured the length, thickness and width of the extra muscular tendon; the length of the intramuscular tendon; muscle fibre length, muscle volume and the length and width of a tear, if present for supraspinatus, infraspinatus and subscapularis muscles. Among the 41 specimens there were 11 shoulders with intact rotator cuff, 12 with partial thickness tears of the cuff and 11 with full thickness tears of the supraspinatus<sup>345</sup>. They reported the tendon thickness to vary from 2.2 mm in normal cuff, 2.4 mm in partial thickness tears and 2.6 mm in cuffs with full thickness tears. They noticed no significant difference in thickness or width between the groups. Roh et al quantitatively described the supraspinatus musculotendinous architecture by harvesting the muscles from 25 embalmed cadavers<sup>15</sup>. They divided each supraspinatus muscle into an anterior and posterior muscle belly on the basis of their fibre insertion. They measured pennation angles and musculotendinous dimensions for each muscle belly, including width, thickness and cross sectional area. They found the mean tendon thickness to be 3.1mm for the anterior part and 2.5 mm for the posterior part.

Vahlensieck et al studied the fibrous architecture of the supraspinatus muscle by comparing 30 MR images and 49 cadaver dissections<sup>344</sup>. They found the supraspinatus muscle to be composed of two distinct portions. They described the mean length of the ventral portion to be 88 mm and of the dorsal portion 106 mm and suggested that both muscle portions probably act differently in moving

the arm. Volk and Vongsness investigated gross and histologic anatomy of the myotendinous portion of the supraspinatus in 20 cadaveric shoulders (10 men and 10 women) with ages ranging from 48 to 76 years<sup>342</sup>. They found that the anterior lateral portion of the supraspinatus contained more tendon than the posterior portion of the muscle in all 20 specimens.

Kim et al performed a three dimensional study of the musculo-tendinous architecture of the supraspinatus tendon<sup>343</sup>. They used ten formalin embalmed male cadaveric specimens (mean age  $61.9 \pm 16$  years) and excluded specimens with evidence of gross shoulder abnormality, previous surgery, or tendon pathology. They performed serial dissection and digitization to collect three-dimensional coordinates (x, y, and z) of the tendon and muscle fiber bundles in situ. The data was then used to reconstruct a three-dimensional model. However, all these studies have been mostly descriptive and have focused on the gross structure of the tendons.

Anatomic studies on elderly cadaveric specimens are unlikely to accurately reflect the tendon structure in individuals who are much younger and who present with shoulder problems in clinical practice. It is well established that the integrity of the rotator cuff decreases with age<sup>124</sup>. Milgrom et al<sup>124</sup> have shown that there is a very significant difference in the incidence of rotator cuff tears in individuals above 50 years of age compared to someone between 30 and 39 for both dominant and non-dominant arms ( $p < 0.001$ ). Their results show that the rotator-cuff lesions demonstrate a statistically significant linear increase with age after the fifth decade of life. Besides, it has been shown that the muscle

volume and the cross sectional area of the rotator cuff muscles were 1.6 times higher in living humans, primarily due to age and dehydration effects<sup>346</sup>.

Therefore, these anatomic data are unlikely to reflect what would be found in young healthy adults.

Turrin and Capello reconstructed a detailed sonographic pattern of the normal supraspinatus tendon and adjacent structures<sup>332</sup>. They imaged the asymptomatic right shoulders of 12 healthy adult volunteers (9 men and 3 women) between 18–47 years of age (mean 35 years) and of a 10- year-old boy. Their study depicted a more complex sonographic pattern of the supraspinatus tendon. The findings in these studies, though insightful are largely descriptive.

Ultrasound has been used to measure the thickness of the supraspinatus tendon in asymptomatic adults<sup>73,193,347-351</sup>. It has also been used to calculate the cross sectional area of the supraspinatus within its fossa in the asymptomatic patient<sup>352,353</sup>. The mean diameter of the supraspinatus tendon has been recorded by ultrasound in these studies as between 4.0- 6.7mm<sup>73,193,347,350,351</sup>. It has been shown to be around 5.2-5.6 mm in the elite baseball athlete<sup>351</sup> and to increase in patients with diabetes<sup>347</sup> and amyloidosis<sup>348</sup>. These studies have assessed the tendon thickness at different points and do not report on the differences between men and women or other rotator cuff dimensions.

Cholewinski et al performed sonographic examination on 36 volunteers (72 shoulders) with no history of shoulder pain as part of their study on the

usefulness of ultrasound measurements in the diagnosis of subacromial impingement of the shoulder<sup>73</sup>. The assessment included measurement of rotator cuff thickness 15 mm posterior to the long head of biceps tendon on the transverse plane and the distance between the infero-lateral edge of acromion and the apex of the greater tuberosity of humerus (AGT distance) with the arm in neutral rotation.

They reported the normal thickness of the supraspinatus as between 4.1 to 6.7 mm with a median value of 6 mm. They did not find any statistically significant difference in rotator cuff thickness between the dominant and non-dominant limb (median difference 0.35 mm). They performed further statistical analysis to find a possible correlation between rotator cuff thickness and age, body mass, height and BMI of the subjects. There was only a tendency for minor correlation between rotator cuff thickness and body mass and BMI, which were not found to be statistically significant (p value respectively 0.08 and 0.09).

Bretzke et al<sup>349</sup> described the characteristic ultrasonographic appearance of normal and pathological rotator cuff in 15 normal volunteers and 48 patients with shoulder pain. They reported that in normal shoulders, the rotator cuff thickness averaged 6 mm at a point 2 cm proximal to the insertion of the supraspinatus tendon while the thickness of the posterior portion, which is thinner than the anterior portion, averaged 3.6 mm. They did not find statistically significant difference between male and females or between left and right shoulders. Additionally, they did not find any correlation between patient age and cuff thickness.

Akturk et al studied the effect of diabetes on tendons, specifically the biceps and supraspinatus as they felt they can be easily measured by ultrasonography<sup>347</sup>. They measured both tendons using high resolution USG in 150 diabetic patients (50 type 1 and 100 type 2 diabetic patients, 75 men and 75 women, mean age 50 years) and 94 control patients (47 men and 47 women, mean age 47 years). They reported the maximal supraspinatus tendon thickness as measured in the longitudinal view, just in front of the lateral part of the humeral head and the transverse thickness of the long head of the biceps tendon in the bicipital groove. They observed a significant increase in supraspinatus and biceps tendon thickness in diabetic patients (Table 4-15). Their study reported tendon thickness in “control patients” but crucially failed to define the control group.

Tendon	Diabetic shoulder	Control shoulder
<b>Right Biceps</b>	4 ± 1.05	2.95 ±0.38
<b>Left Biceps</b>	4.04 ±1.02	2.97 ±0.26
<b>Right Supraspinatus</b>	6.60 ±1.25	4.91 ±0.41
<b>Left Supraspinatus</b>	6.58 ±1.18	4.96 ±0.39

**Table 4-15: Tendon thickness in diabetic and control shoulders**

Jadoul et al<sup>348</sup> performed a cross-sectional ultrasonographic evaluation of supraspinatus tendon and femoral neck capsule thickness in 49 patients on long-term haemodialysis to look for beta 2-microglobulin (beta 2M) infiltration of joint synovia, tendons and capsules as part of dialysis related amyloidosis. As part of the study they also measured the supraspinatus tendon thickness in 30 controls on their dominant side. The thickness ranged from 4.5 to 7.8 mm (6.3 ±0.8 mm) in the control subjects. They did not find a significant correlation with

body weight, height, age or gender. They noticed that the thickness of the supraspinatus tendon and the femoral neck capsule increased significantly with the duration of the dialysis.

Wallny et al<sup>350</sup> calculated the diameter of the rotator cuff as a mean of three measured values, at intervals of 1 cm, in the transverse scans of the tendons of supraspinatus and infraspinatus. They reported the mean diameter of the rotator cuff to be 6.25 mm and found no significant differences between men and women or between the dominant and non-dominant side. O'connor et al<sup>193</sup> measured supraspinatus tendon thickness in 11 asymptomatic volunteers and reported a mean value of 4.87 mm.

Wang et al<sup>351</sup> performed sonographic assessments to compare the thickness of biceps and supraspinatus tendons in the shoulders of elite college baseball athletes (injured and uninjured) and healthy controls. Members of the control group were completely asymptomatic and had no history of shoulder pain or injury did not participate in sports at a professional level and were matched in physical characteristics with the recruited athletes. This study found thicker supraspinatus tendons in elite injured (5.6 mm) and uninjured (5.2 - 5.4 mm) baseball athletes compared with the control group (4.0 - 4.2 mm). There were no professional athletes in our group, for us to make a comparison.

The present study has for the first time demonstrated the mean and range of dimensions of the rotator cuff in the young healthy adult. It has demonstrated that except for thickness of the supraspinatus tendon at the footprint, the

dimensions between dominant and non-dominant hands are not statistically significantly different. There is a statistical difference between the dimensions of females and males for all measurements. Even where there is a statistically significant difference between the dominant and non-dominant arms, the absolute difference in value is very small to make a clinical difference. This is important as it means that an asymptomatic contra-lateral shoulder can be used as a guide to estimate normal dimensions of the affected shoulder. Our results add to previous studies which showed no significant difference in supraspinatus thickness between the dominant and non-dominant side<sup>73,348</sup>.

Partial thickness tears are classified arthroscopically using the Ellman grading<sup>354</sup>, which is based on a supraspinatus thickness of 10-12mm just proximal to its insertion on to the humerus. There is no evidence for using this as a reference range. Our study has documented the width of the supraspinatus footprint in a younger population who are most likely to suffer from a partial thickness tear. This information will be helpful in determining the percentage of the tendon involved in partial thickness tear at arthroscopy. Although there is a wide range in the data, our study has shown that the contralateral shoulder can and should be used as a control in almost all circumstances supporting the argument for always performing bilateral shoulder ultrasounds.

This study has also shown that the rotator cuff measurements cannot be correlated with an individual's height or weight. Other studies have come to the same conclusion<sup>73,348</sup>. While most studies did not look at the differences between

men and women for the tendon thickness, the two studies that reported them did not find statistically significant difference between the genders<sup>348,350</sup>.

There are certain limitations to our study. The volunteers for our study were all chosen from our institution. There are no reasons to believe they will be any different to the general population. The technique of ultrasonography is highly user dependent<sup>187,195,355</sup>. Previous studies using ultrasound to measure the thickness of tendons have shown that even with well-defined protocols substantial inter-observer and to a lesser extent intra-subject inter-visit variation exists<sup>193</sup>. In our study, the Bland-Altman plots show good agreement for both inter and intra-observer measurements, supporting the use of ultrasound to image the shoulder. It must be noted that all the measurements in our study were made in asymptomatic volunteers from a younger age group who are unlikely to have rotator cuff pathology. The rotator cuff is known to display thinning with advancing age<sup>73</sup>, and therefore this data cannot be extrapolated to other age categories. Future studies may look at the normal dimension of other age groups, for example 41-60, 61-70, 71-80 years. We believe this study has made a start at the documentation of normal shoulder anatomy by ultrasound.

## 4.5 Conclusion

This study has shown the normal dimensions of the rotator cuff for subscapularis, supraspinatus and infraspinatus in young adults. A normal reference pattern will be helpful in clinical practice as the appearance of the rotator cuff often lacks detail because of varying degrees of degeneration in patients referred for shoulder ultrasonography. There is a wide range in the rotator cuff measurements, which makes using classifications based on an average size difficult. The study reassures us of the reliability of shoulder ultrasound measurements and emphasises the utility and appropriateness of routine screening of the other shoulder as a control.

## Chapter 5 Microvascular blood flow in normal and pathological rotator cuff

### Summary:

*In this chapter, I will provide a comprehensive literature review on the vascularity of the rotator cuff and its implications for the pathogenesis of rotator cuff tears. This provides the rationale for my in vivo Laser Doppler Flowmetry study on the microvasculature of normal and a spectrum of pathological rotator cuffs. This chapter provides a detailed description of the study aims, methods and results.*

### Declarations:

*The laser doppler probe placements were done intraoperatively by the operating surgeons Mr Steve Drew and Mr Tom Lawrence. The candidate collected data. Dr Nicholas Parsons advised on statistics.*

### This work has been published

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### This work has been presented

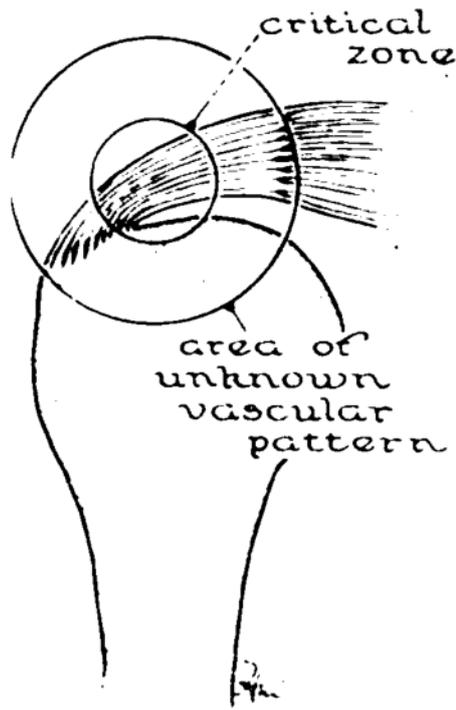
*Microvascular blood flow in normal and pathological rotator cuff.*

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## 5.1 Introduction

The role played by vascular supply in the pathogenesis of rotator cuff disease has fascinated many investigators. Vascular insufficiency has been proposed as one of the aetiologies for rotator cuff pathology<sup>17,21-23</sup>. According to this theory, reduced blood flow to certain areas of the tendon causes vascular compromise which may lead on to pain, tendinopathy, poor tendon healing and ultimately tears in some cases. In 1934, Codman<sup>28</sup> was the first to describe a watershed area in the rotator cuff with poor perfusion. He described this hypovascular area, later called the “critical zone” as being in the distal 10mm of the tendon near its insertion onto the greater tuberosity of the humerus<sup>28</sup> (Figure 5-1). He noted that this region tended to be anaemic with a gross appearance suggestive of an infarction. There is no consensus on whether there is a ‘critical area’ of relative avascularity in the supraspinatus tendon that makes it vulnerable to tendinopathy and eventual tears<sup>18,19,21-27</sup>.

Although significant advances have been made in the management of rotator cuff pathology, they have come about without a clear understanding of the role played by vascularity in its pathogenesis<sup>17</sup>. In this chapter, I will first discuss what is currently known about the vascular supply of the rotator cuff, the discrepancies in the literature about the presence and extent of a “critical zone” and microvasculature of the rotator cuff. This will form the foundation for my observational study on microvasculature of normal and a range of pathological rotator cuffs using Laser Doppler Flowmetry (LDF) intraoperatively.



**Figure 5-1: Diagram of rotator cuff insertion. Encircled areas indicate: 1) Critical zone and 2) Area of unknown vascular pattern (from: Moseley and Goldie<sup>24</sup>)**

### 5.1.1 Arterial supply

Blood supply to the rotator cuff primarily comes from six arteries, as per Rothman and Parke<sup>22</sup>. In their anatomic study on shoulders from 44 term foetuses and 28 representatives from all decades of life they found that the suprascapular, anterior circumflex humeral and posterior circumflex humeral arteries were present in 100% of cases<sup>22</sup>(Figure 5-2). In addition, they found that the thoracoacromial, suprahumeral and subscapular arteries contribute to the rotator cuff in some cases. Chansky and Iannotti<sup>17</sup> also found that the most consistent gross arterial supply of the rotator cuff is by the anterior humeral circumflex artery and the suprascapular artery which supplies the anterior portion of the rotator cuff, while the posterior humeral circumflex artery supplies the posterior portion of the rotator cuff.



**Figure 5-2: Arterial supply of the rotator cuff: *Left*-Anterior circumflex humeral artery. *Right*-Posterior circumflex humeral artery (1), Suprascapular artery (2). (source: Rothman and Parke<sup>22</sup>)**

Moseley and Goldie<sup>24</sup> found that the anterior humeral circumflex, suprascapular and subscapular arteries are the main contributors to the rotator cuff. According to them, the rotator cuff derives its blood supply from osseous, muscular and tendinous vessels. The osseous supply is by a branch from the anterior circumflex humeral artery, which penetrates the insertion of the tendinous portion of the rotator cuff and anastomoses with the vascular network of the tendinous portion. The muscular vessels were derived from the suprascapular and the subscapular arteries and form an anastomotic network through the musculotendinous junction into the tendon. They also found that the tendinous portion was well vascularised and remains so throughout life. No sex differences were noticed.

Although there is some agreement about the main arterial supply of the rotator cuff, differences persist about the microvascular blood flow and the presence and extent of the critical zone. These discrepancies come from studies that have reported conflicting results.

### 5.1.2 Critical zone

The concept of a hypovascular “critical zone” with decreased or absent vascularity is primarily supported by in-vitro studies<sup>18,19,21-23</sup>. A study by Moseley and Goldie was the only one histological study that did not support the idea of a hypovascular critical zone<sup>24</sup>. Most of these earlier studies were performed by first injecting cadavers with a mixture of a hardening substance like latex and an opaque agent to enhance imaging. The tissues were then subsequently imaged and tissue samples taken for detailed histologic assessment. It has been argued that there are inherent weaknesses with these injection techniques<sup>20</sup>. Firstly, the injection process itself can create problems like micro emboli limiting capillary filling in the tendon<sup>20,23</sup>. Secondly, it has been suggested that it is very difficult to align the vascular pattern with the histological appearance of the same part of the tendon<sup>23</sup>.

Later studies using in-vivo physiological techniques like ultrasound and Doppler failed to support the presence of a “critical zone” in the rotator cuff <sup>25-27,131</sup>.

	Critical zone present	Critical zone absent
In vitro studies	Lindblom <sup>356</sup> Rothman <sup>22</sup> Rathbun <sup>23</sup> Fukuda <sup>133</sup> Ling <sup>18</sup> Lohr <sup>21</sup> Determe <sup>19</sup> Brooks <sup>357</sup>	Moseley <sup>24</sup>

<p style="text-align: center;"><b>In vivo studies</b></p>	<p style="text-align: center;">Biberthaler<sup>135</sup> Rudzki<sup>132</sup></p>	<p style="text-align: center;">Swiontkowski<sup>27</sup> Silvestri<sup>26</sup> Levy<sup>25</sup> Funakoshi<sup>131</sup> Matthews<sup>67</sup></p>
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**Table 5-1: List of studies on rotator cuff vascularity**

### 5.1.3 In vitro studies

#### 5.1.3.1 Supporting critical zone

As early as 1939 Lindblom described areas of relative avascularity in the supraspinatus tendon adjacent to its point of insertion<sup>356</sup>. Rothman and Parke<sup>22</sup> studied shoulders from 44 term fetuses and 28 representatives from all decades of life. Under controlled pressure, a mixture of latex and India ink was injected into the arterial system of the specimens. The injection mixture was solidified by subsequently perfusing the specimen with 10% formalin. The rotator cuff was dissected, photographed, sectioned and stained for histologic examination. They noticed a markedly under vascularized area in relation to the rest of the cuff, in the distal part of the supraspinatus tendon and just proximal to its insertion (Figure 5-3). They reported that serial histological sections confirmed that the area is truly hypovascular and not an artefact of the injection technique.



**Figure 5-3: Hypovascular area in the supraspinatus tendon (circled) - supero lateral view of the right shoulder (source: Rothman and Parke<sup>22</sup>).**

Rathbun and Macnab<sup>23</sup> carried out their studies on cadavers as soon after death as possible. 500 millilitres of a 20% suspension of micropaque was injected into the subclavian artery. This was followed by an injection of 900 millilitres of a 20% suspension of micropaque in 5% gelatin. The individual muscles with their bony attachments were dissected free, fixed in formalin and decalcified. They noticed a constant area of relative avascularity related to an area extending from a centimetre away and up to its point of insertion (Figure 5-4). This zone of relative avascularity was present in specimens of all ages, even in cadavers

under the age of twenty. This zone of avascularity was constantly seen only in the supraspinatus tendon, whereas the other tendons comprising the rotator cuff showed good filling of the vascular bed. Although the method they employed did not avoid the inherent weakness of the injection technique of embolization, they were able to demonstrate constantly 15 to 20 micron calibre vessels.



**Figure 5-4: The microvascular pattern of the supraspinatus tendon. The arrow points to the zone of avascularity near the tendon insertion (source: Rathbun and Macnab<sup>23</sup>)**

Fukuda et al studied histologic sections from 12 en bloc surgical specimens of patients with partial bursal-sided rotator cuff tears (BSRCT)<sup>133</sup>. The specimens included the bony insertion, the partially torn cuff and the musculotendinous junction of the supraspinatus tendon. The specimens were fixed in 10% buffered formalin, decalcified in formic acid and stained with azan or haematoxylin and eosin. On histologic examination, they noticed that all the tears developed within 1 cm of the tendon insertion and that the proximal stump was uniformly avascular, confirming the inherent hypovascularity of this area. The vascularity was normal more proximally, around the musculotendinous junction.

Ling et al noticed an avascular zone on the surface of the middle of the supraspinatus tendon with its external edge at a mean distance of 7.8 mm from the osteo-tendinous attachment<sup>18</sup> (Figure 5-5). They studied twenty fresh cadaveric shoulders in two age groups (Ten aged 18-45 years and ten above 55 years; five males and five females in each group). The brachial artery was injected with a solution of gelatin and India ink and the rotator cuff was dissected. They then studied the vascular sources and the anastomosis in the supraspinatus tendon, the size and location of the critical zone and the shortest distance between the critical zone and the osteo-tendinous attachment. They noticed that there were extensive anastomoses of the blood vessels at the osteo-tendinous and the musculo-tendinous junction but very little at the critical zone. They also report that the histologic sections showed that the critical zone was not an artificial by-product of the injection technique.



**Figure 5-5: \* denotes the area of hypovascularity in the supraspinatus tendon. Branches from 1-anterior circumflex humeral artery. 2-subscapular artery. 3-posterior circumflex humeral artery (source: Ling et al<sup>18</sup>).**

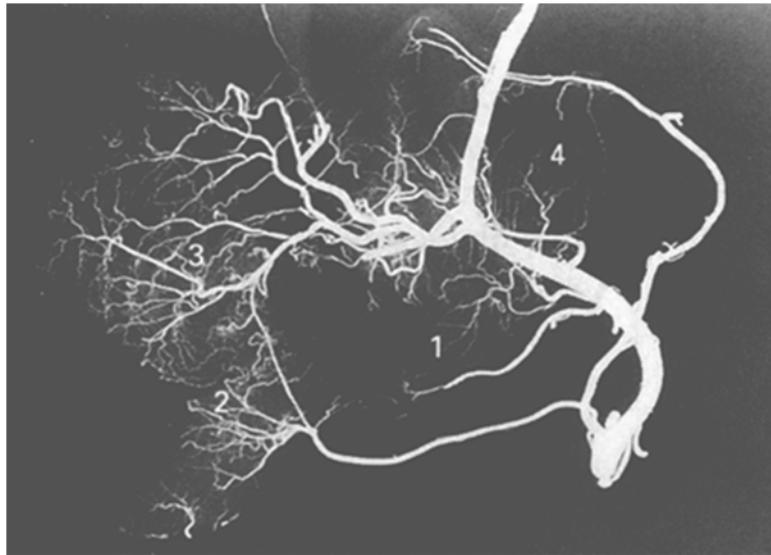
Lohr and Uhthoff studied the vascular pattern of the supraspinatus tendon in eighteen human anatomic specimens, which ranged in ages from 26 to 84 years<sup>21</sup>. They did selective vascular injection with a silicon-rubber compound allowing visualisation of the vascular bed of both the supraspinatus tendon and the humeral head. Their study confirmed the presence of a hypovascular zone in the supraspinatus tendon close to its insertion into the humeral head. They also noticed that the articular side of the tendon is at a disadvantage compared to the bursal side, which appears to be relatively well vascularised (Figure 5-6).



**Figure 5-6: A transverse section of the supraspinatus tendon with bursal side superior, articular side inferior and the humeral head at right inferior. Arrows point to the area of hypovascularity at the articular surface (source: Lohr and Uhthoff<sup>21</sup>).**

Determe et al studied 25 shoulders in which the rotator cuff was devoid of macroscopic lesions from unembalmed cadavers within 48 hours post mortem<sup>19</sup>. They concluded that there is a very real critical zone with a reduced blood flow about 1.5 cm from the greater tubercle. They are of the view that this area represents the zone of convergence of the anterior and posterior circumflex humeral artery, the suprahumeral and the thoracoacromial artery (Figure 5-7).

Histologic studies on six specimens confirmed the poor vascularity of this critical zone. This critical zone was present irrespective of the age of the cadaver.



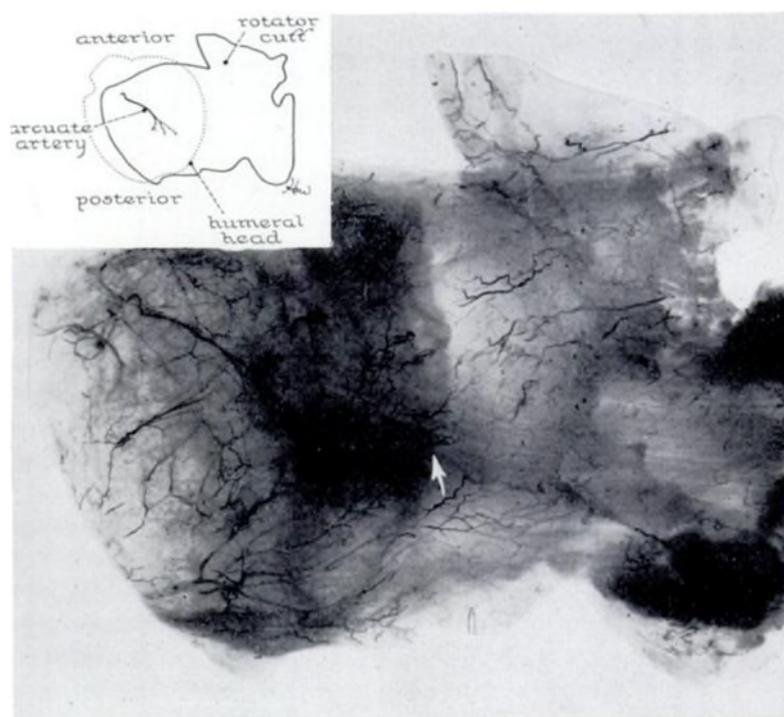
**Figure 5-7: Vascularity of critical zone. 1 - Area of convergence, 2 - Supraspinatus muscle, 3 - infraspinatus muscle, 4 - subscapularis muscle (source: Determe et al<sup>19</sup>).**

Brooks et al performed a quantitative histological analysis of the vascularity of the supraspinatus and infraspinatus tendons<sup>357</sup>. They measured vessel numbers, size and percentage of the tendon occupied by vessels at 5 mm intervals from the tendon insertions to the muscle bellies proximally. They noticed no significant differences between the vascularity of supraspinatus and infraspinatus and that both tendons were hypovascular in their distal 15 mm.

#### **5.1.3.2 Not supporting critical zone**

This concept of an avascular critical zone did not receive support from only one histological study. Moseley and Goldie performed an injection study of the vascular pattern in seventy-two shoulders<sup>24</sup>. They injected a mixture of gelatin, potassium iodide, barium sulphate and formalin into the first part of the subclavian artery, which was then examined macroscopically and in some instances, histologically. The specimens were also assessed photographically and

radiologically. Their study of the morphologic pattern of the arteries in the rotator cuff conclusively showed that the “critical zone” of the rotator cuff corresponds to the zone of anastomosis between the osseous and tendinous vessels but did not find any evidence that the critical zone is much less vascularised than any other part of the tendinous cuff<sup>24</sup> (Figure 5-8). This study had a high dropout rate due to technical problems, beginning with seventy-two shoulders but reporting on the findings of only six.



**Figure 5-8: The vascular pattern in the tendinous portion of the rotator cuff. The arrow shows one of many zones where superficial and deep vessels anastomose. Inset: Diagram for orientation (from: Moseley and Goldie<sup>24</sup>)**

#### **5.1.4 In vivo studies**

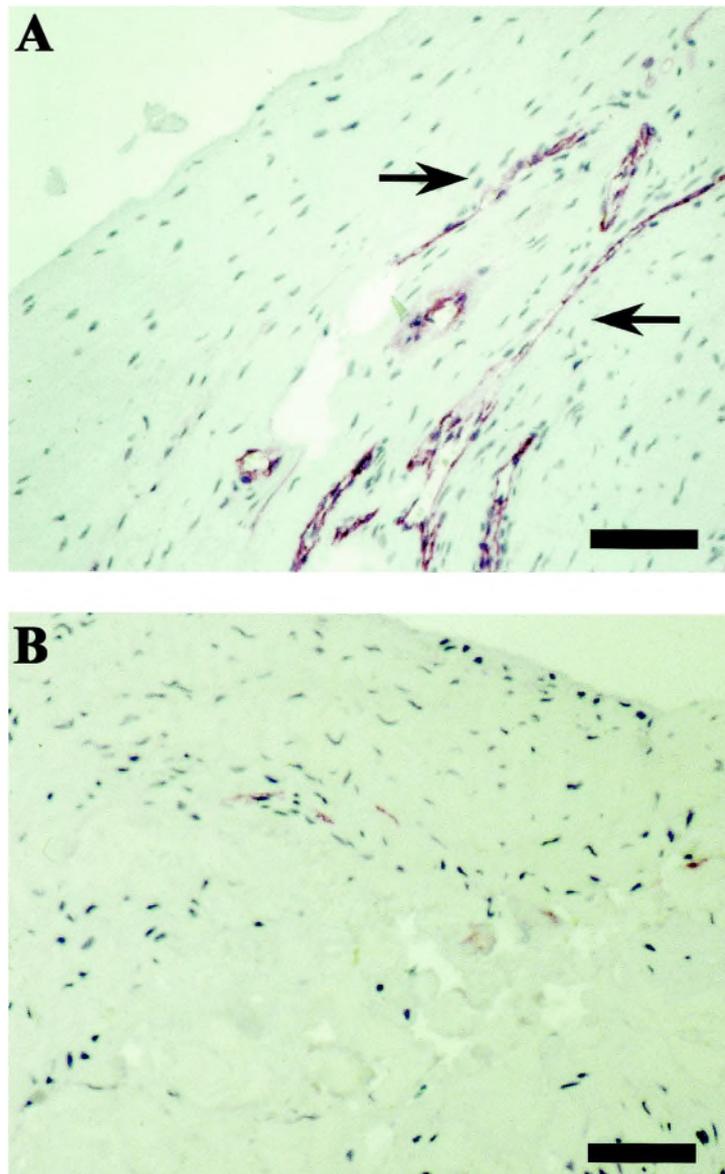
Recent studies on rotator cuff blood flow have used newer technologies like Doppler Ultrasonography<sup>131,132,358</sup>, Laser Doppler flowmetry<sup>25,27</sup> and Orthogonal polarisation<sup>135</sup>, a microscopic technique which uses reflected polarised light in patients having arthroscopic surgery. The arrival of Doppler technology has given researchers a relatively inexpensive and at the same time a versatile, non-

invasive method by which vascularity in living tissues can be measured. The chief advantage of these newer technologies is their ability to visualise microvasculature in vivo.

In general, studies performed in vivo question the validity of the concept of a critical zone in the supraspinatus tendon, with some exceptions. An in-vivo study by Biberthaler et al<sup>135</sup> and another study published twice by Adler et al and Rudzki et al (these two publications used the same data from a single study) supported the concept of an avascular critical zone.

#### **5.1.4.1 Supporting critical zone**

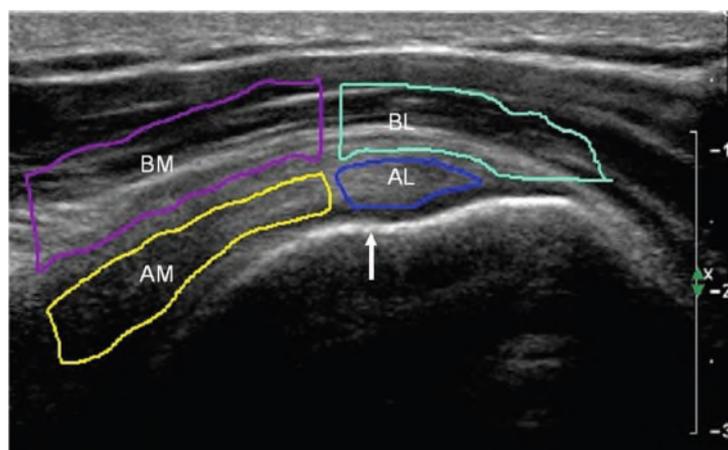
Biberthaler et al used orthogonal polarization spectral imaging, which allows noninvasive, quantitative assessment of the human microcirculation without application of fluorescent contrast medium within an arthroscopic setting<sup>135</sup>. They studied eleven patients with clinical signs of a degenerative rotator cuff lesion. Functional capillary density and capillary diameter were studied in vivo during shoulder arthroscopy. After the images were recorded, biopsy specimens of 1 mm<sup>2</sup> were taken from the scanned regions and were immunostained against CD31. The functional capillary density in areas close to rotator cuff lesions was found to be significantly reduced ( $20 \pm 14$  cm/cm<sup>2</sup>) compared with  $106 \pm 13$  cm/cm<sup>2</sup> in control areas in the unaffected tendon insertion zone. Further in vitro analysis of specimens taken from the scanned regions using quantitative histological techniques showed that the number of capillaries in the critical zone was reduced to almost half of that of the controls (Figure 5-9).



**Figure 5-9: Immunohistochemical staining of microvessels. Specimen taken from a control region (A) shows several microvessels (arrows) whereas no microvessels are seen in the specimen taken from a region adjacent to the lesion (B) (source: Biberthaler et al<sup>135</sup>)**

In the Adler/Rudzki et al study<sup>132,358</sup>, 31 asymptomatic volunteers with an intact rotator cuff aged between 22–65 years (mean age, 41.5 years) underwent lipid microsphere contrast-enhanced ultrasound of a randomly selected shoulder. Among the 31 volunteers, sixteen were younger than forty years and fifteen older than forty. Images from the volunteers were obtained at baseline, after contrast administration with the subject at rest and after contrast administration

after the subject had exercised. Quantitative analysis of data was performed from four regions of interest (ROIs): bursal medial, articular medial, bursal lateral and articular lateral (Figure 5-10). The plane of the anatomic neck was used as the boundary between the medial and lateral parts of the tendon and a median line through the long axis of the tendon separated the articular surface from the bursal surface. The bursal ROIs also included the adjacent peritendinous blood vessels.



**Figure 5-10: ROIs used for analysis of blood flow. Bursal medial (BM), bursal lateral (BL), articular medial (AM) and articular lateral (AL) ROIs are shown. Arrow points to the plane of the anatomic neck (from: Adler et al<sup>358</sup>).**

Analysis of blood flow at the four ROI s consistently showed a region of reduced vascularity at the articular medial margin of the rotator cuff. The blood flow in this region was significantly less compared to the bursal medial ( $p=0.002$ ) and the bursal lateral ( $p=0.003$ ) zones and the difference approached significance ( $p=0.052$ ) compared to the articular lateral zone. After exercise, a 59%-96% increase in enhancement was noticed for all the regions combined. Still, the articular medial region had significantly reduced flow compared with all other ROIs ( $p<0.002$ ). In their view the study showed diminished vascularity in the articular portion of the supraspinatus tendon, in keeping with the concept of a critical zone.

#### *5.1.4.2 Not supporting critical zone*

Swiontkowski et al used laser Doppler flowmetry (LDF) to investigate rotator cuff vascularity in vivo<sup>27</sup>. Eleven men and four women aged between 39 to 68 years undergoing open surgical procedures for rotator cuff disease were studied. Among the fifteen, four had stage I disease, three had stage II and eight had stage III or complete cuff tear, as per Neer's definition<sup>9</sup>. The LDF measurements were made on the bursal surface of the tendon at multiple points. The output signal is proportional to the blood flow and was expressed as the blood cell flux (BCF).

They observed that subacromial impingement produces a hyperaemic response within the impingement zone of the tendon. As the disease progresses to stage II (partial tear and fibrosis), significant blood flow was observed at the edges of the partial tear in all patients. Finally, they noticed that when these untreated partial tears progress to a complete tear, the hyperaemic response persists in an attempt to heal the complete tear. They concluded that impingement may produce a hyperaemic response, which by resorption of damaged collagen fibres may ultimately lead to partial or complete tear of the supraspinatus tendon rather than any 'avascular zone' in the tendon<sup>27</sup>. They acknowledge that lack of background BCF data in normal rotator cuff for comparison is a problem, but since this was an invasive technique, no data was available on blood flow in non-pathologic rotator cuffs.

Slvestri et al<sup>26</sup> assessed nineteen patients with rotator cuff pathology and six asymptomatic shoulder controls using a power Doppler ultrasound. He performed a spectral analysis of flow signals in vivo and noticed the presence of

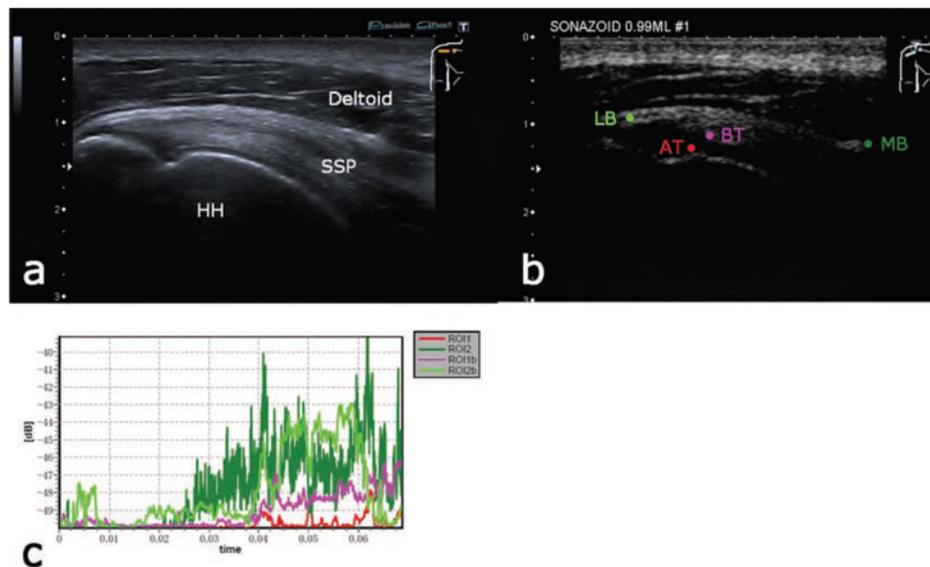
vascularity and microvessels at or near the tear site in patients with partial or complete rotator cuff tear. He did not describe a critical or hypovascular zone, but observed that blood flow in a normal tendon may be too weak to be detected by ultrasound.

Levy et al<sup>25</sup> used laser Doppler flowmetry (LDF) during arthroscopic shoulder surgery to study the microcirculation of the normal rotator cuff and to investigate if it is altered in pathologic conditions. They measured blood flow in six different regions of each rotator cuff in 56 consecutive patients undergoing arthroscopic surgery for management of impingement, rotator cuff tears or instability. They found that the mean LDF flux was significantly higher at the edges of a complete tear compared with normal cuffs ( $p = 0.0089$ ). In patients with impingement the LDF flux was significantly lower across all regions of the cuff compared with normal cuffs ( $p = 0.0196$ ) and torn cuffs ( $p < 0.0001$ ).

Although LDF analysis of the rotator cuff blood supply indicated a significant difference between the vascularity of the normal and the pathological rotator cuff, they were unable to demonstrate a functional hypoperfusion area or so-called 'critical zone' in the normal cuff. They observed that although the measured flux decreases with advancing impingement, there is a substantial increase of blood flow at the edges of rotator cuff tears. They postulated that this might reflect an attempt at repair of the tear.

Funakoshi et al<sup>131</sup> examined the differences in microvascularity using contrast enhanced ultrasound (CEUS) between the intact rotator cuffs of young and

elderly people and between intact and torn cuffs in elderly people. Ten volunteers (all men) with an intact rotator cuff and fifteen patients (10 men and 5 women) with a rupture supraspinatus tendon on one shoulder and a continuous tendon on the other shoulder were studied. They analysed four regions of interest (ROI) – the articular side of the tendon (AT), the bursal side of the tendon (BT), the medial side of the bursa (MB) and the lateral side of the bursa (LB). They used relatively small ROIs and examined it intensively to visualise the vascular pattern in detail. Analyses were performed using time intensity curves in a blinded fashion (Figure 5-11).



**Figure 5-11: Ultrasound of an asymptomatic shoulder. B mode image (a); HH-Humeral head, SSP-supraspinatus tendon. Contrast enhanced ultrasound (CEUS) image (b); AT-articular side of tendon, BT-bursal side of tendon, LB-lateral side of bursa, MB-medial side of bursa. Time intensity curves for each region of interest (ROI) of CEUS (from: Funakoshi et al<sup>131</sup>).**

A comparative study of the blood flow between the 4 ROIs showed that in all groups the blood flow within the supraspinatus tendon (AT and BT) was significantly lower ( $p < 0.0001$ ) compared with the blood flow noted in the subacromial bursal tissue (MB and LB). There was no significant difference in the vascular distribution inside the supraspinatus tendon (AT vs BT). There was also

no significant difference in blood flow inside the tendon between the groups with intact cuffs and the group with rotator cuff tears. They did observe an age-related decrease in blood flow for the intratendinous tissue.

Matthews et al<sup>67</sup> studied cellular and vascular changes in different stages of full thickness rotator cuff tears. They took biopsies from the supraspinatus tendon in forty patients who were undergoing surgery for chronic rotator cuff tears and compared them with biopsies taken from four uninjured subscapularis tendons. They used monoclonal antibodies directed against leucocytes, macrophages, mast cells and vascular markers. They noticed that small sized rotator cuff tears showed increased fibroblast cellularity, blood vessel proliferation, vascular markers and the presence of a significant inflammatory component indicating a potential to heal. These reparative changes diminished as the size of the rotator cuff tear increased.

Goodmurphy et al<sup>134</sup> performed immunocytochemical analysis on rotator cuff tendons to compare normal cadaver shoulders with age matched live subjects who underwent surgery for rotator cuff tears. They noticed no significant difference in the vascularity of the surgical specimens at the edge of the tear (i.e. <2.5 mm from the tear margin) and the matched cadaveric controls. There appears to be hypervascularity in sections taken 2.5 to 5 mm away from the tear compared to sections taken from either cadaveric or surgical specimens within 2.5 mm of the tear ( $p < 0.001$ ). They found no differences in nuclear distribution patterns or in the ability to produce procollagen between surgical specimens from sites near the tear or away from the tear. In their conclusion, they state,

“these data suggest that the rotator cuff in the vicinity of either a complete or intrasubstance tear is, in fact, not hypovascular. The avascularity of the critical zone, may be an artifact of techniques used during prior cadaveric studies”.

It is important to note that almost all the in-vivo studies that did not find evidence for the presence of a critical zone were conducted in patients with a pathological rotator cuff. This may support the argument that pathology changes the blood flow in the rotator cuff irrespective of a critical zone in the normal rotator cuff.

Although both extrinsic and intrinsic theories have been proposed as the possible aetiology of rotator cuff tears<sup>9,55,62</sup>, most authors currently believe that intrinsic tendon degeneration probably linked to micro-vascular disturbances predominates<sup>58,121,122,359</sup>. Thus, enhancing knowledge regarding the micro-vascular blood flow of the rotator cuff is essential in further understanding the pathological processes. While some anatomical studies have shown a consistent crossover of blood vessels across the osteotendinous junction in supraspinatus<sup>360</sup>, others have shown that almost no vessels are present distally at the articular surface of the tendon<sup>21</sup>. Most cadaveric studies<sup>21-23</sup> have documented the poor microvascular supply within the supraspinatus tendon but in-vivo measurements have contradicted these findings with an increase in blood flow on the edge of a full thickness tear<sup>25-27,131</sup>.

Rotator cuff vascularity plays an important role in the rehabilitation and surgical interventions that are chosen to treat cuff pathology<sup>20</sup>. The potential role of

vascularity in the pathogenesis of rotator cuff tendinopathy requires further study, as it may have important implications for understanding the natural history of the disease and the development and application of surgical and biologic interventions. As such, the vascularity of the rotator cuff remains an important question to answer.

Hegedus et al conducted an extensive literature review on vascularity and tendon pathology in the rotator cuff<sup>20</sup>. Their review included 19 studies, of which 10 were carried out on cadavers (in vitro), six on live subjects (in vivo) and three studies examined both cadavers and live subjects. They looked at reasons for the conflicting findings in the literature and analysed the studies to see if these differences could be attributed to limitations in older lower technology injection studies performed in cadavers or to the arm position, which could influence the rotator cuff blood flow. They concluded that neither technology nor arm position during infusion seem to be the reason for the divergent results of these 19 studies. It could be that the quality and methodology of these studies were so variable that conflicting results were only to be expected.

They observed that there is no large sample, in-vivo study that uses the best technology to compare pathological with non-pathological shoulders. They recommended further larger sample, in-vivo, Doppler studies comparing normal and the spectrum of pathological cuffs to clarify the results regarding the presence of a critical zone.

In-vivo studies have inherent advantages, not the least of which is better

generalisability of results than cadaver studies. Advances in Doppler ultrasound instruments and techniques have improved the detection of small vessels. Further, low-volume and slow-flowing vessels can be visualized better by increasing the signal-to-noise ratio using microbubble-based USG contrast agents. However, Laser Doppler flowmetry may be the most sensitive tool to detect microvasculature, finding vessels as small as 0.01 mm in diameter.

I designed an observational study to measure the blood flow in both normal and a range of pathological rotator cuffs using an in-vivo laser Doppler probe. This technique will allow an accurate assessment of the microvascular blood supply of living tissue. The study will measure blood flow in five different regions of the cuff within each individual and will compare to assess variability between and within individuals.

## **5.2 Study design**

### **5.2.1 Ethics approval**

The study was reviewed and approved by the Coventry and Warwickshire Research Ethics Committee (REC Reference number: 10/H1211/42) (Appendix: I)

### **5.2.2 Sponsorship and funding**

The study was sponsored by two collaborating organisations: University of Warwick and University Hospitals Coventry and Warwickshire NHS Trust (Appendix: J). The study had funding from the Academy of Medical Sciences.

### **5.2.3 Patient recruitment**

All adult patients having arthroscopic shoulder surgery under the care of two shoulder surgeons (Mr Steve Drew and Mr Tom Lawrence) at University Hospitals Coventry and Warwickshire NHS Trust were potentially eligible. All patients presented to the clinic with shoulder pain related to the rotator cuff (except the control group). Everyone had symptoms for a minimum of 3 months and had a course of conservative management, which included analgesia, physiotherapy and subacromial injection(s). The diagnosis of subacromial impingement was made by an experienced consultant shoulder surgeon in patients who had a painful arc and positive impingement signs, but with no radiological or intra-operative evidence of a cuff tear. There were no acute traumatic cuff tears in the group.

Study participants were categorized into four groups based on their intra-operative diagnosis:

- (i) Normal rotator cuff and undergoing surgery for unrelated pathology (stabilisation and labral repairs) (Control Group)
- (ii) Subacromial Impingement syndrome
- (iii) Partial thickness rotator cuff tears
- (iv) Full thickness rotator cuff tears

Measurements were taken from thirty consecutive patients in each group giving a total of 120 patients for the study.

#### **5.2.3.1 Inclusion criteria**

Patients who were able to give informed consent and having one of the following procedures were considered eligible to be included in the study.

- a) Patients with full thickness rotator cuff tears (up to 2 cm) undergoing an arthroscopic rotator cuff repair
- b) Patients with partial thickness rotator cuff tears undergoing arthroscopic subacromial decompression
- c) Patients with impingement syndrome undergoing arthroscopic subacromial decompression
- d) Patients with shoulder pathology not related to the rotator cuff undergoing arthroscopic procedures (e.g. arthroscopic stabilization and SLAP repair).

#### **5.2.3.2 Exclusion Criteria**

- a) Patients unable to give informed consent
- b) Patients under 18 years of age

- c) Patients who have undergone previous shoulder surgery
- d) Patients with co-morbidities that may affect micro-vascular blood flow (e.g. patients with diabetes, inflammatory arthritis, synovitis or adhesive capsulitis)
- e) Patients with massive (defined as cuff tears of more than 2 cm) or irreparable cuff tear

### **5.2.3.3 Consent**

Eligible patients were approached prior to the procedure and the study was explained to them in detail. They were also given a participant information sheet (Appendix: K) to keep, which provided details about the study. Informed consent (Appendix: L) was obtained from all the participants, after allowing sufficient time for the patient to consider their decision and ask questions about the procedure. Participants were told that they were free to withdraw from the study at any time, without giving any reason and that this will not affect the standard of care they receive.

### **5.2.4 Outcome measures**

The outcome measure for the study was the blood flow as recorded by the laser Doppler probe. This was expressed as perfusion units on a scale from zero to 1000 at each of the five standardized positions within the rotator cuff.

### **5.2.5 Data management**

All data were immediately transferred to a digital format. The patient-identifiable information was held on a secure, password-protected database accessible only to essential personnel. Patients were identified by a code number only. Direct access to source data was required for study related

monitoring. The electronic data will be retained for at least five years after the completion of the study.

### 5.2.6 Laser Doppler Flowmetry

Laser Doppler is a standard technique for the non-invasive blood flow monitoring and measurement of blood flow in the microcirculation. The laser Doppler technique measures blood flow in the very small blood vessels of the microvasculature. The tissue thickness sampled is typically 1mm, the capillary diameter 10 microns and the velocity spectrum measurement typically 0.01 to 10mm/s. The technique depends on the Doppler principle whereby low power light from a monochromatic stable laser, e.g. a Helium Neon gas laser or a single mode laser diode, incident on tissue is scattered by moving red blood cells and consequently is frequency broadened. The frequency-broadened light, together with laser light scattered from static tissue, is photo detected and the resulting photocurrent processed to provide a blood flow measurement<sup>361</sup>.

Perfusion measurements using fiber optic laser Doppler monitors have been made on practically all tissues and applied in most branches of medicine and physiology<sup>362-365</sup>. The term commonly used to describe blood flow measured by the laser Doppler technique is 'flux': a quantity proportional to the product of the average speed of the blood cells and their number concentration (often referred to as blood volume). This is expressed in arbitrary 'perfusion units'.

Standardisation of LDF instrument measurements in perfusion units can be achieved by measuring a flux due to the Brownian motion of particles in a motility standard comprising polystyrene microspheres in water.

### 5.2.6.1 LDF monitor

The moorVMS-LDF laser Doppler blood flow monitor (Moor instruments Ltd., Millway, Devon, UK) is a high performance medical grade instrument for clinical and research applications<sup>25</sup>. It uses a semiconductor laser diode to generate laser radiation with a wavelength of  $785 \pm 10$  nm and a maximum power output of 2.5 mW. This low power laser light is transmitted via an optic fibre to a VP3 Needle probe (Moor instruments Ltd., Millway, Devon, UK), which has an external diameter of 1.5 mm and length of 80 mm (Figure 5-12).



**Figure 5-12: LDF monitor with memory chip probes.**

The moor VMS-LDF monitor comes with a digital LCD screen display but does not have an internal memory. The monitor was therefore connected to a laptop running the moorVMS-PC software via the USB probe to permanently record the trace and storage of data for subsequent analysis. The advanced windows compatible moorVMS PC software comes with extensive analytical features and automatic report generation. It offers marker and ROI (Region of interest) functions for flexible analysis (Figure 5-13).

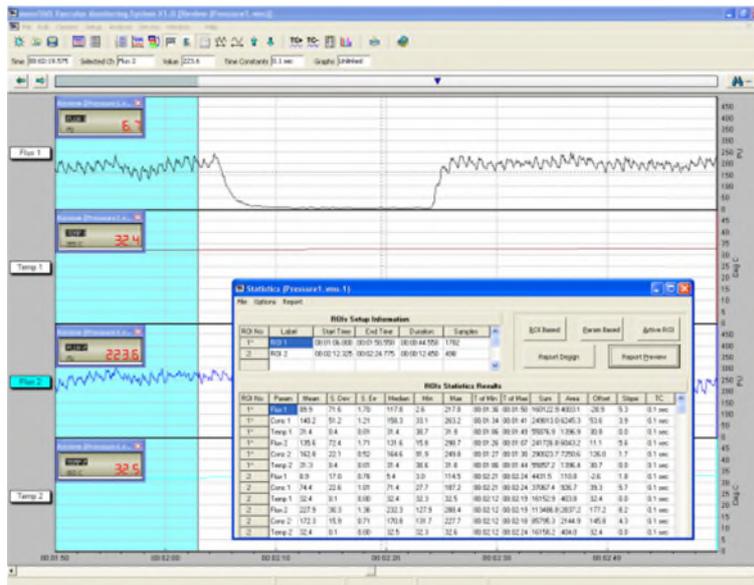


Figure 5-13: A screen shot from the moorVMS PC software

### 5.2.6.2 Laser Doppler probes

The VP3 needle probes are amongst the most versatile designs. They can be used for surface measurements or inserted into tissues. The compact design helps with measurements in deeper tissues with restricted access. It has a hypodermic stainless steel tube with an external diameter of 1.5 mm. There is 0.5 mm separation between the fibres. They are available in various lengths from 10 to 80 mm. We used the probes with a length of 80 mm. These “MemoryChip probes” have a memory chip inside which stores the calibration constants for each probe with timed recalibration reminders within the probe itself. As these “MemoryChip probes” store their individual calibration information within the connector itself, when the probes are changed between patients, the correct calibration data for that specific probe is always applied automatically.

### 5.2.6.3 Calibration

The probes were calibrated regularly using a calibration kit supplied by the manufacturer. The calibration kit consists of a probe-flux standard, a probe clamp, optical paper for cleaning the probe tip, and calibration instructions (Figure 5-14). The probe-flux standard uses the Brownian motion of polystyrene microspheres in water to provide the standard reference when calibrating probes. Care was taken to maintain the room temperature as close to the same each time the probe was calibrated. Calibration was also a good indicator of the probe condition, as a damaged probe would not calibrate.



Figure 5-14: VP3 Needle probe calibration kit

### 5.2.6.4 Sterilisation

The probes were sterilized using the STERRAD system<sup>366</sup>. It uses low temperature, hydrogen peroxide gas plasma technology to sterilize a wide range of instruments efficiently, effectively and safely. The technology is particularly suited to the sterilization of heat and moisture sensitive instruments since process temperatures do not exceed about 50 degrees C (140 degrees F) and sterilization occurs in a low moisture environment. Vaporized hydrogen

peroxide is introduced into a vacuum chamber. Plasma is generated to safely eliminate residual hydrogen peroxide. The process produces non-toxic by-products like oxygen and water, which are safe for the environment. The efficacy of the process has been demonstrated against a broad spectrum of microorganisms and on a large number of substrates used in medical instruments<sup>366,367</sup>. This dry, low temperature process produces gentle sterilization for the most delicate products potentially leading to longer instrument life.

## 5.2.7 Intervention

### 5.2.7.1 *Intraoperative ultrasound*

At the start of the trial, we planned to use an ultrasound probe intra-operatively to assess the rotator cuff for intrasubstance tears and guide probe placement for articular sided partial thickness tears. A microsurgery guidance transducer (UST-533, Hitachi Aloka) was identified as the optimal probe due to its extra small footprint. The UST-533 probe was a linear array transducer with a frequency range of 13.33-4.4 Mhz and provided a scan width of 10 mm (Figure 5-15).



**Figure 5-15: UST-533 ultrasound probe**

The probe had an optional handling tool and together with it the probe can be handled as if holding a pencil between the fingers. The probe was used in conjunction with an Aloka SSD-3500SX Prosound scanner (Aloka Co.Ltd, Tokyo, Japan). The prosound scanner is a compact and easy to use diagnostic ultrasound system.

During the arthroscopic procedure, the ultrasound probe was introduced through the standard lateral portal to assess the integrity of the cuff and identify partial thickness cuff tears (Figure 5-16). The position of any intrasubstance or articular sided partial tears was documented and then a laser Doppler probe was introduced through the same lateral portal and five standardized measurements were taken of the rotator cuff blood flow.



**Figure 5-16: Intraoperative ultrasound of the rotator cuff**

However, we experienced several practical difficulties with this approach:

1. The subacromial space was too narrow for the proper placement of the transducer

2. The transducer provided a scan width of only 10 mm, which was too narrow to provide any meaningful information. The probe had to be moved along the tendon multiple times and this greatly increased the operating time.
3. It was not possible to introduce and hold the ultrasound probe and the laser Doppler probe in the subacromial space simultaneously.
4. A larger skin incision was necessary to introduce the transducer in the subacromial space, which compromised the therapeutic part of the arthroscopic surgery as it was impossible to maintain the fluid pressure in the subacromial space.
5. The intraoperative ultrasound probe provided very little additional information as arthroscopy provided a good view of both the articular and the bursal surfaces of the cuff and the preoperative ultrasound with its better resolution provided information on intrasubstance tears.

We therefore decided not to continue using an intraoperative ultrasound probe.

#### **5.2.7.2 Blood flow measurements**

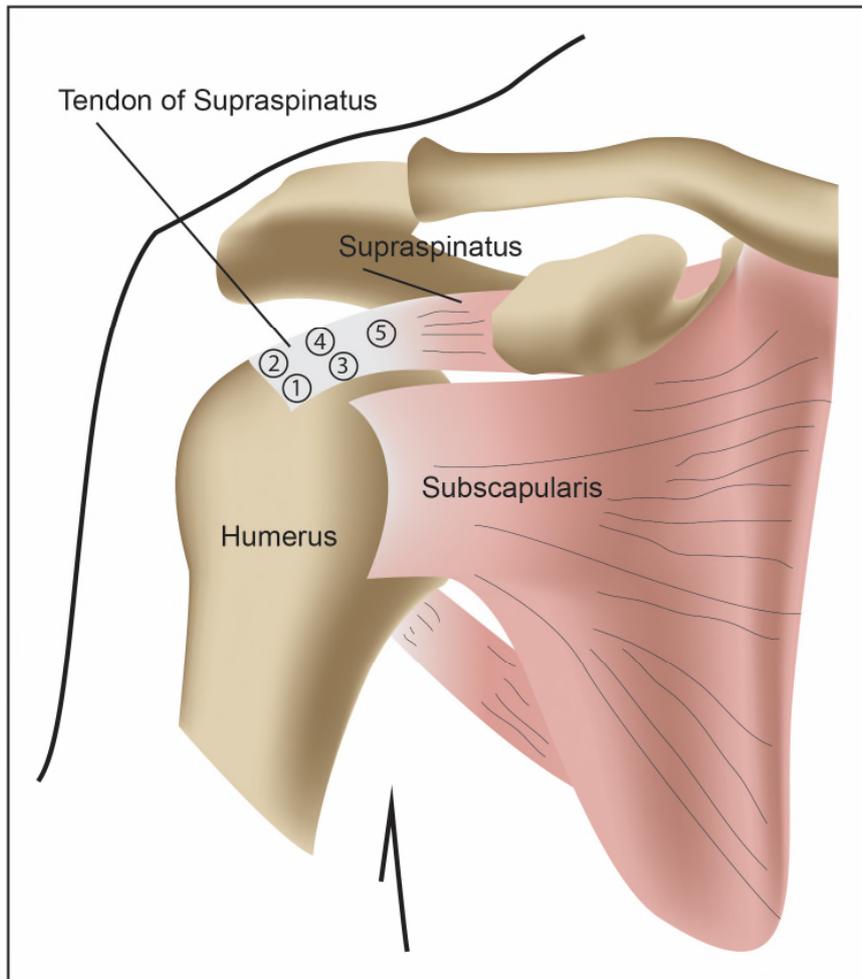
All patients had their operations under general anaesthesia. An inter-scalene nerve block was administered by the anaesthetist for post-operative pain relief, in line with our normal practice. Patients were sat up in the beach chair position. The operation was performed without any traction to the upper limb and with the arm on the side of the body. A saline irrigation pump was used to control the fluid pressure throughout the procedure.

Each patient included in the trial underwent a full arthroscopic assessment through standard arthroscopic portals in-line with current practice prior to commencing a therapeutic procedure. Diagnostic arthroscopy was used to confirm the exact pathology associated with the rotator cuff i.e. subacromial impingement with an intact rotator cuff, partial thickness rotator cuff tear or a full thickness rotator cuff tear. After diagnostic arthroscopy, a laser Doppler probe (Moor VP3 probe, Moor instruments Ltd, Axminster, Devon, U.K.) was introduced either through the existing lateral portal or by using a 16G needle as a conduit through the skin into the subacromial space. The microvascular blood flow was then measured in 5 different regions on the bursal side of the rotator cuff under direct vision. The blood flow measurements were taken before any therapeutic interventions were undertaken. Under standard conditions, measurements were made for 30 seconds in each of the zones after a steady trace was observed.

The regions (zones) are as shown in Figure 5-17:

1. Antero-lateral cuff (at its insertion)
2. Postero-lateral cuff (at its insertion)
3. Antero-medial cuff (1 cm medial to insertion)
4. Postero-medial cuff (1 cm medial to insertion)
5. Musculo-tendinous junction.

For the group with full thickness tears, the anterolateral and posterolateral measurements were taken at the edges of the tear. The anteromedial and posteromedial measurements were taken a cm medial to the lateral points.



**Figure 5-17: Blood flow measurement areas on the rotator cuff: 1- anterolateral, 2- posterolateral, 3- anteromedial, 4- posteromedial and 5- musculotendinous.**

To eliminate artefacts during the measurement, the intensity of the arthroscopic light source was turned to minimum and the saline irrigation pump was stopped to ensure normal physiologic pressure in the subacromial space. Care was taken to avoid pooling of blood at the measurement site and the lead was secured to minimize any movement. The mean systemic arterial pressure was maintained between 70 – 80 mm Hg throughout the measurements. The LDF monitor was connected to a laptop running the moorVMS-PC software and the data was captured, stored and analysed. Output was measured as “flux” and expressed in perfusion units, which is proportional to the speed and concentration of red blood cells in the tissue.

### 5.3 Statistical analysis

Data were summarized by calculating means and standard deviations, and presented graphically using box and scatter plots. Exploratory linear regression analysis was used to quantify the relationship between age and blood flow, and t-tests and chi-squared tests were used to assess differences between study groups.

An adjusted stratified analysis of variance (ANOVA) procedure was used to assess differences in blood flow between zones (1-anterolateral, 2-posterolateral, 3-anteromedial, 4-posteromedial and 5-musculotendinous) within individuals and between groups of individuals (i-normal, ii-impingement, iii-partial tear and iv-full tear). The two strata identified in the analysis were associated with comparisons between individuals (diagnosis groups) and within individuals (zones). Analyses were such that effects for both groups and regions were partitioned into single degree of freedom contrasts that allowed assessment of each hypothesis; e.g. for groups this meant that the three degrees of freedom for comparing groups were split into single contrasts reporting (i) normal *versus* impingement, (ii) normal *versus* partial tear and (iii) normal *versus* full tear. F-tests were used to assess statistical significance, which was set at the 5% level.

#### 5.3.1 Null hypothesis

Our null hypothesis was that there is no difference in the micro-vascular blood flow in patients with normal rotator cuffs compared to patients with pathological

rotator cuffs. We also hypothesised that there is no difference in the micro-vascular blood flow between different regions of the rotator cuff.

## 5.4 Results

The demographics of the study population are shown in Table 5-2. The group with the normal rotator cuff was predominantly male (chi-squared test;  $p=0.008$ ) and significantly younger than the other groups (t-test;  $p<0.001$ ).

	Normal	Impingement	Partial tear	Full tear
<b>Age</b>				
Mean (sd)	30 (7.8)	55 (10.3)	57 (13.1)	63 (10.1)
(Range)	(18-48)	(35-78)	(26-80)	(45-88)
<b>Sex</b>				
Male: Female	24:6	14:16	19:11	12:18

**Table 5-2: Demographics of study population. Age is expressed in years as mean with standard deviation (sd) and range. Sex distribution is expressed as a ratio**

Data were analysed after logarithmic transformation to improve the normality assumptions required for ANOVA and linear regression (Figure 5-18: Histogram after logarithmic transformation of flux values).

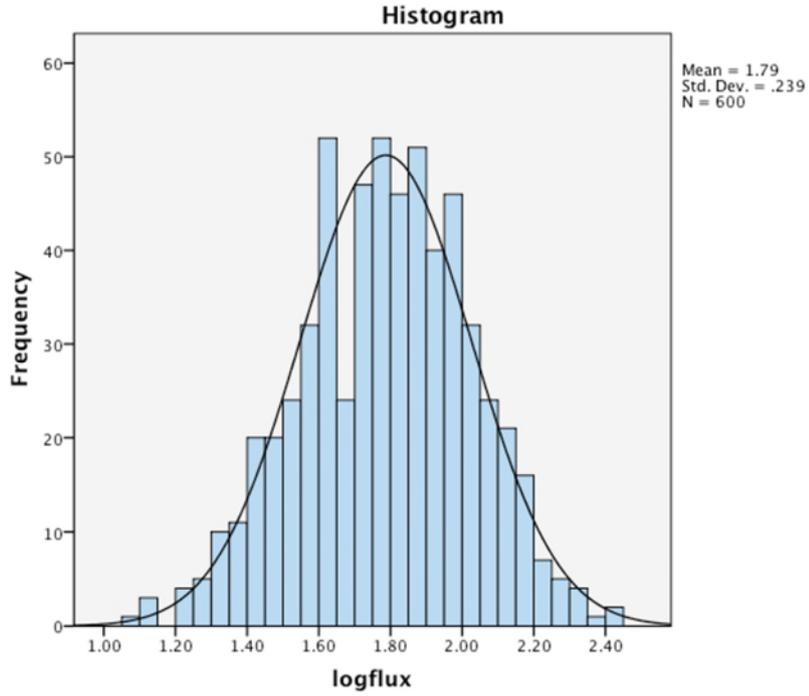


Figure 5-18: Histogram after logarithmic transformation of flux values

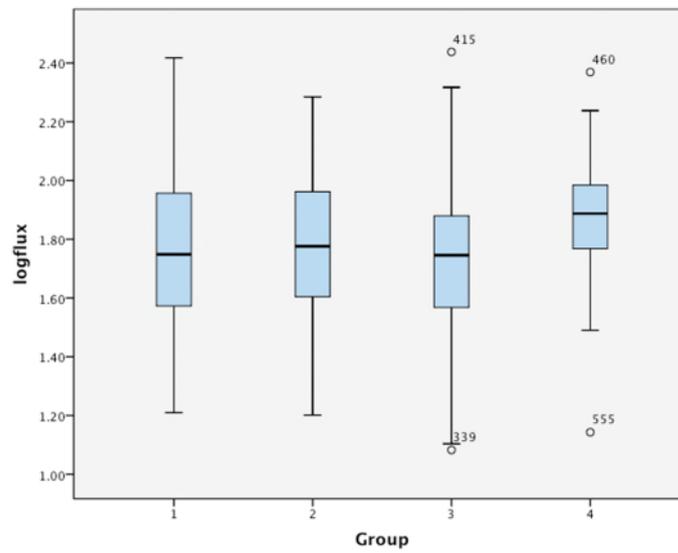
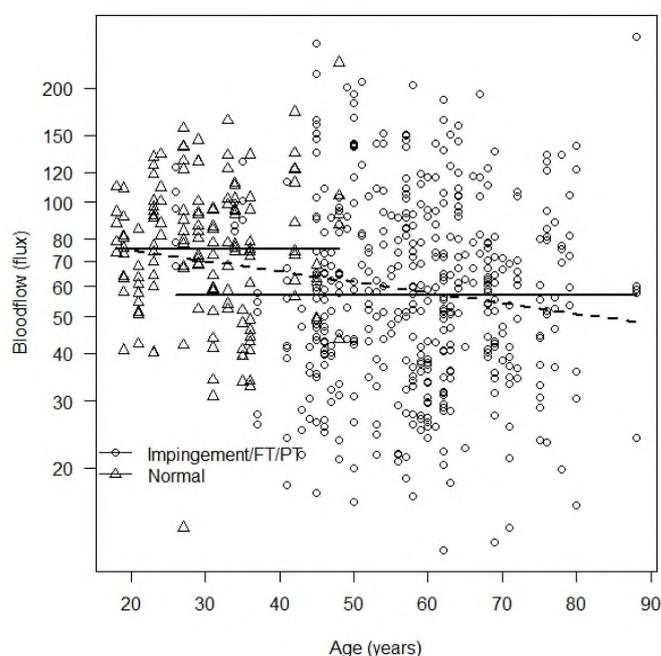


Figure 5-19: Boxplot of log transformed values for each group. 1-Impingement, 2-Partial thickness tears, 3-Full thickness tears, 4-Normal cuff

### 5.4.1 Variation in blood flow with age

A full understanding of the relationship between age and blood flow is, in part, compromised by the large differences in both age and blood flow between the study groups (i.e. Normal, Impingement, Partial Tear (PT) and Full Tear (FT)).

A linear regression analysis showed what superficially appeared to be a negative association between age and blood flow (i.e. blood flow decreased with age), was actually nothing more than an artefact of the grouping. That is, an analysis of the relationship between blood flow and age within study groups (normal and other groups) showed that regression coefficients were zero, indicating that there was no evidence for an association between age and blood flow within any of the groups (Figure 5-20). There was no evidence that blood flow differed between genders (t-test;  $p=0.858$ ).



**Figure 5-20: Scatter plot of blood flow versus participant age for normal and non-normal groups. A linear regression ignoring groups ( - - ) showed a significant negative association between age and blood flow ( $p<0.001$ ). However, adding an interaction term to this model showed that the association was purely between groups ( $p=0.003$ ), as the regression coefficients within groups were zero (—).**

### 5.4.2 Variation in total blood flow between groups

The analysis of variance (ANOVA) indicated that the total blood flow measured across all regions was greater in the group with the normal rotator cuff compared to the groups with the pathological rotator cuff (ANOVA F test; F value 10.8;  $p=0.001$ ). This is apparent by simply looking at the raw data plots in Figure 5-21. Among the pathological groups, the largest effect was seen between the group with normal cuff and the group with full thickness tears (ANOVA F test; F value 7.25;  $p=0.008$ ); however, overall there was no strong evidence to suggest important differences in blood flow between the pathological groups.

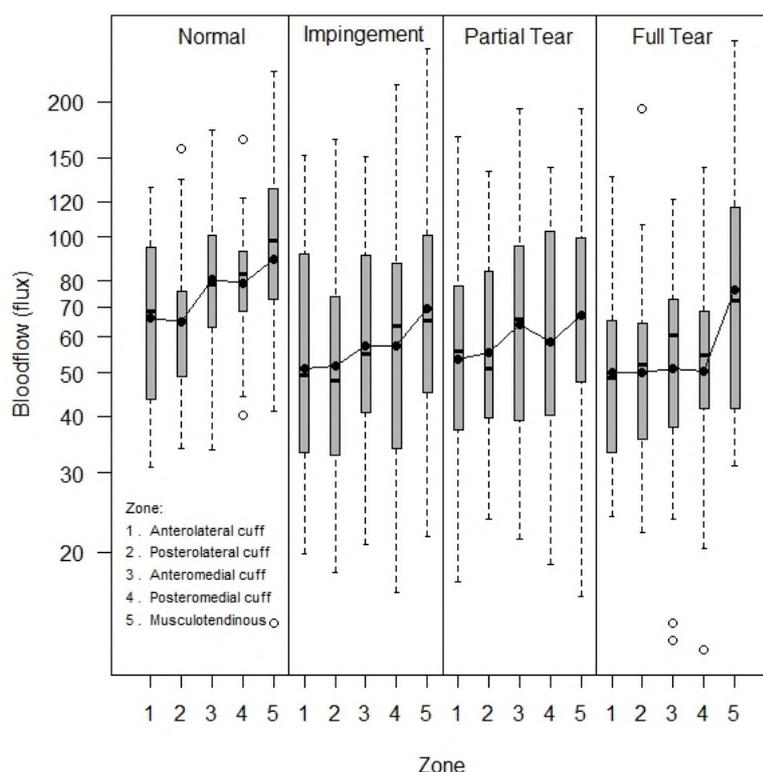


Figure 5-21: Boxplots for each group and zone, with means (•); the vertical axis is plotted on a log scale, as this was used for the analysis to improve normality assumptions. Box represents the interquartile range (IQR), whiskers represent 1.5 times the IQR and o represent outliers beyond 1.5 times the IQR.

### 5.4.3 Variation in blood flow between zones

There were significant differences in blood flow between the 5 zones. (Figure 5-21). Blood flow was highest at the musculotendinous junction (Zone 5) compared to the blood flow in the tendinous part (Zones 1-4). This difference was highly significant (ANOVA F test; F value 42.34;  $p < 0.001$ ) and this effect was observed consistently across all four groups. Analyses of measurements within the tendinous part across all the four groups indicate that blood flow in the lateral insertional part of the tendon (Zones 1 and 2) was overall significantly less (ANOVA F test; F value 9.79;  $p=0.002$ ) than the medial part (Zones 3 and 4). It also indicated that the pattern of blood flow between zones was almost equivalent for normal, partial tear and impingement groups, but was different for the full tear group ( $p=0.020$ ). In the full tear group, we saw no great difference between Z1, Z2, Z3 and Z4, but all these are much lower than Z5.

### 5.4.4 Variation in blood flow between zones and across groups

Analysis of the blood flow at individual zones between the groups has shown that the blood flow was significantly lower at the anteromedial and posteromedial cuff (Zones 3 and 4) in the group with impingement (ANOVA F tests; Zone 3,  $p = 0.010$  and Zone 4,  $p=0.028$ ) and full thickness tears (Zone 3,  $p = 0.015$  and Zone 4,  $p=0.042$ ) compared to the group with normal cuff. This difference at zones 3 and 4 did not reach statistical significance in the group with partial thickness tears (Zone 3,  $p=0.562$  and Zone 4,  $p=0.273$ ). Although we note that analyses using data from individual zones only is weaker than analyses using all the data together, so the inferences we make are more tentative.

Region	Group			
	Normal	Impingement	Partial tear	Full tear
<b>Anterolateral</b>	71.61 (61.24, 81.99)	61.02 (46.71, 75.34)	61.35 (48.85, 73.85)	56.99 (45.06, 68.92)
<b>Posterolateral</b>	69.23 (58.63, 79.82)	61.74 (46.91, 76.57)	62.01 (50.37, 73.65)	56.40 (44.09, 68.70)
<b>Anteromedial</b>	85.83 (74.35, 97.32)	64.93 (52.83, 77.03)	74.93 (58.91, 90.96)	57.69 (48.20, 67.18)
<b>Posteromedial</b>	82.31 (73.06, 91.56)	72.67 (53.28, 92.05)	67.56 (54.24, 80.87)	58.62 (46.87, 70.38)
<b>Musculotendinous</b>	99.71 (83.66, 115.76)	81.85 (62.42, 101.28)	77.72 (62.20, 93.23)	92.29 (69.14, 115.43)
<b>Mean</b>	81.74 (76.41, 87.07)	68.44 (61.39, 75.5)	68.71 (62.69, 74.74)	64.40 (57.8, 71.0)

**Table 5-3: Mean flux values (with 95% confidence intervals) for the four groups at each region.**

## 5.5 Discussion

In our study, the cumulative blood flow measured across all regions was highest in the group with the normal rotator cuff. The total blood flow was lower in all the groups with a pathological rotator cuff (subacromial impingement, partial thickness tear and full thickness tear) with the lowest values in the group with full thickness tears (

Table 5-3). We are aware that the group with the normal rotator cuff were significantly younger compared to the pathological group. Although Rudzki<sup>132</sup> and Funakoshi<sup>131</sup> have shown an age related decrease in intratendinous vascularity of the supraspinatus using contrast-enhanced ultrasound, our data showed no strong evidence that blood flow decreased significantly with age. Our results are similar to Levy et al who also used LDF and found that the total blood flow was significantly lower in the group with pathologic cuffs and that age and gender were not significant predictors of blood flow in the tendon<sup>25</sup>.

Our results also demonstrate that the blood flow is not uniform throughout the tendon. The blood flow is highest medially at the musculotendinous junction and is lower laterally, with the lowest values seen at the point of insertion of the tendon on to the bone (Figure 5-21). Within the control group, blood flow was significantly higher at the musculotendinous junction (zone 5) compared to the medial part of the tendon (zones 3 and 4), which in turn was significantly higher than the lateral part of the tendon (zones 1 and 2). These results would be expected in any muscle- tendon- bone transition, with the muscle having the most vascularity and decreasing as the tissue becomes more tendinous<sup>38</sup>. It does

not support a 'critical zone' of avascularity in the mid-substance of the tendon. Many histological studies have described a markedly hypovascular area compared to the rest of the tendon in the distal part of the supraspinatus tendon and just proximal to its insertion<sup>21-23</sup>. Moseley has shown that the “critical zone” corresponds to the zone of the anastomoses between the osseous and the tendinous vessels but found no evidence that it is much less vascularized than any other part of the tendinous cuff<sup>24</sup>. All these injection techniques have an inherent weakness in that injected suspensions of any material always form emboli at the capillary level of the vascular bed, as acknowledged by Rathbun<sup>23</sup>. Recently, contrast enhanced ultrasound (CEUS) has been used to study blood flow in the rotator cuff. Adler<sup>358</sup> found regional variations in the intratendinous blood flow with the lowest values at the articular medial margin of the rotator cuff, while Funakoshi<sup>131</sup> did not find any significant difference in the vascular distribution within the supraspinatus tendon. Using LDF, Levy et al<sup>25</sup> were unable to find a “critical zone” in the supraspinatus tendon. Similar results were seen in the Achilles tendon, where LDF has shown that blood flow is lower near tendon insertion<sup>38</sup>.

Across the groups the difference in blood flow was pronounced mainly in zones 3 and 4, where it was significantly lower in the groups with impingement and full thickness tears compared to the normal group. The difference was not significant in the partial thickness tear group. This could be postulated that the impinged cuff is at risk of tear due to a decreased blood flow phenomenon and that the torn cuff has a response to tear with an increase blood flow. Hyper vascularity at the edge of partial thickness tears was noted by Fukuda et al<sup>133</sup> on histology and

Swiontkowski et al<sup>27</sup> by LDF. Although, Levy et al have shown higher blood flows at the edges of a full thickness cuff tear<sup>25</sup>, in our study we did not see this response in full thickness tears. Matthews et al<sup>67</sup> have shown increased blood vessel proliferation and fibroblast cellularity in small sized rotator cuff tears but as the tear size increased there was a trend towards reduced vascularity.

This study adds to that of Levy et al on some findings: the total blood flow was significantly lower in the group with impingement and that age and gender were not significant predictors of blood flow in the tendon. Likewise, both studies agree that there is no evidence of a “critical zone”. Levy et al found an increase in blood flow in all regions on the bursal surface (including the musculotendinous junction) in the group with cuff tears compared to the group with normal cuff. In our study the blood flow in all pathological rotator cuff groups were lower than the group with normal cuffs. Our study also differs to that of Levy et al, as it demonstrated a decrease in blood flow in the more lateral positions and where the cuff is more tendinous. This would reflect what would be expected in a normal musculo-tendinous transition.

Although, the LDF technique we used was like the one described by Levy et al, there were important differences in the methodology of our study. There were four well-defined groups in our study with equal number of participants in each group. These groups included patients with normal rotator cuff and a spectrum of pathologic rotator cuffs ranging from subacromial impingement (with no rotator cuff tear) to full thickness rotator cuff tears. Unlike Levy et al, we have split the cuff tears group into full and partial thickness tears to define whether

there is a difference between these two sub-groups. We have also defined exactly where measurements were taken in relation to the tear. Also, in the series by Levy et al, the measurements were made with the patients lying on their side and the arm abducted to 30 degrees without any local or regional nerve blocks. In our series, the patients were sat in the beach chair position with the arm by their side and all had an interscalene nerve block. These factors may account for the differences in the results from the two studies.

Of the 30 patients with partial thickness tears in our study, 27 had articular-sided partial thickness tears and 3 had bursal-sided partial thickness tears. Although, the pathology of bursal-sided and articular-sided tears may be different, as there were only three bursal-sided tears it makes analysis of this subgroup difficult.

It has been proposed that the position of arm may be a contributing factor for the presence of a critical zone of hypoperfusion. Rathbun and Macnab suggested the 'wringing out' theory<sup>23</sup>. They thought it is possible that the constant pressure exerted by the humeral head on the supraspinatus tendon might "wring out" the vessels in this area. They noticed that there was almost complete filling of all the blood vessels throughout the tendon all the way to its insertion when they performed their injection study with the shoulder passively abducted, thereby relaxing tension on the supraspinatus. They found support for this theory by the fact that the subscapularis tendon, which normally has an abundant blood supply, showed an area of relative hypovascularity near its insertion when putting the shoulder in forced external rotation stretched the tendon. Similar

results were seen in the intra-capsular portion of the biceps tendon, which is stretched over the head of the humerus like the supraspinatus. In our study, all measurements were made with the arm by the side of the body in the beach chair position. Blood flow was not measured by changing upper limb posture for this study, but is a very interesting theory that future studies could address.

We believe that this is the first study to directly compare the micro-vascular blood flow in normal rotator cuffs with a spectrum of pathological rotator cuffs, particularly studying partial thickness tears as a separate group, using a physiological in vivo technique, which allowed real time measurement of blood flow. We were also able to demonstrate variability in the rotator cuff blood flow within individuals and across different groups. The main limitation was our inability to age-match the groups. Ethical considerations for an in vivo study meant the control group with normal rotator cuffs could only comprise of patients who were having arthroscopic surgery for an alternative diagnosis with no obvious pathology of the rotator cuff. This group therefore had patients mainly undergoing stabilization surgery who were younger and predominantly male. The other limiting factor is that, currently LDF does not provide an absolute measure of blood perfusion; therefore, making it difficult to make a direct comparison of values obtained by other methods, but did allow comparison between the groups in our study.

## 5.6 Conclusion

Real time in-vivo laser Doppler analysis has shown that the microvascularity of rotator cuff is not uniform throughout the tendon. There are regional variations with the lowest blood flow found at the point of insertion of the tendon suggesting that a 'critical zone' of hypovascularity medial to its insertion may not exist. The total blood flow in the supraspinatus tendon was found to be significantly lower in the pathological tendon compared to the normal tendon, with the lowest values seen in patients with full thickness tears.

The issue of rotator cuff vascularity in terms of both normal and pathological conditions remains controversial to date. This in-vivo study with reasonable sample sizes in each comparative arm addresses some of those controversies.

## Chapter 6 Conclusions

### 6.1 Summary of new findings

Rotator cuff pathology is responsible for significant disability among patients of all ages. Most patients' symptoms get better after a period of conservative management either in primary or secondary care setting. Conservative management includes physiotherapy and drugs, most commonly corticosteroids or NSAIDs administered either orally or parenterally. Corticosteroids are generally administered as a subacromial injection while NSAIDs are usually taken orally and both these approaches have the potential to cause serious side effects. There are theoretical advantages to use NSAIDs as a subacromial injection but its efficacy was unknown.

Chapter 3 of this thesis discusses the two-common group of drugs used in the treatment of subacromial impingement syndrome and the rationale for a subacromial NSAID injection. The double blind randomised controlled trial comparing subacromial methylprednisolone with subacromial tenoxicam injection presented in this thesis is the first study to directly compare a subacromial corticosteroid injection with a subacromial NSAID injection to treat subacromial impingement syndrome, although corticosteroids and NSAIDs are the two most common drugs used for this condition. The study has shown that local injection of tenoxicam is safe and well tolerated but despite its theoretical advantages a single subacromial injection of 20 mg was not as effective as methylprednisolone in improving shoulder function at 6 weeks.

During the study, I realised that there were still diagnostic challenges particularly in the use of ultrasonography to evaluate the integrity of rotator cuff. Chapter 4 has demonstrated that ultrasonography is increasingly used to evaluate rotator cuff pathology due to its many advantages. It is highly accurate in detecting full thickness tears but much less so in detecting partial thickness tears. A review of our own practice has shown that the sensitivity is lower to detect partial thickness tears by ultrasonography than that for full thickness tears (Appendix A). This thesis has documented for the first time the normal ultrasound dimensions of the subscapularis, supraspinatus and infraspinatus along with deltoid and biceps tendon in a group of asymptomatic young adults under the age of forty years. Establishing normal reference values is important as it aids in identifying pathology. The observational study in chapter 4 has shown that the dimensions between men and women vary significantly but for the same individual the dimensions of both shoulders are comparable. This is important as each patient can be their own control and their contralateral shoulder can be used as a reference. This thesis has also shown that repeat ultrasound measurements are reliable between observers and between visits.

As part of the study, I wanted to explore factors associated with the pathogenesis of rotator cuff tears. Although early descriptions of rotator cuff tears and impingement lesions focussed on external compression of the bursa and tendons, the observation that most supraspinatus tears occur at a region just proximal to its insertion into the humerus led to the concept of an avascular zone in the supraspinatus tendon. Anatomic or physiologic reduction in microvascular blood flow to localised areas of supraspinatus tendon has been implicated as a

factor in initiating or contributing to rotator cuff pathology. For many years, the presence of a critical zone in the supraspinatus tendon has been well established in the medical literature, supported mainly by in vitro histologic studies on cadaveric specimens, as discussed in chapter 5. Recently, this concept has been challenged with the introduction of new physiological in-vivo techniques. One of the aims of this thesis, was to find out the pattern of microvascular blood flow in normal and a spectrum of pathological rotator cuffs. New information presented in chapter 5 of this thesis shows that in living humans, the microvascular blood flow is not uniform in non-pathological supraspinatus tendons, but is similar to what can be expected in a normal muscle-tendon-bone interface. I found no evidence for a localized hypovascular or avascular zone in normal supraspinatus tendons. I explored the blood flow in patients with partial thickness tears as a separate group for the first time and found it to be similar to the group with impingement syndrome; both with lower values compared to the group with normal tendons group but higher than that of the group with full thickness tears. Hypervascularity, postulated as a sign of healing was not demonstrated at the edges of either partial or full thickness tears in our study.

These findings along with established research discussed in Chapter 2 suggest that the development of rotator cuff tears may not be related to the presence of a critical zone alone and that other factors in addition to microvascularity have a role in the initiation and progression of rotator cuff pathology. The use of an intraoperative ultrasound probe caused lots of practical difficulties with very little benefit.

## 6.2 Implications and future directions

Painful shoulders are a significant socioeconomic burden. The aetiology for subacromial impingement syndrome is multifactorial. It is likely that inflammation and oedema in the subacromial bursa and the rotator cuff tendons are responsible for pain. Although in our trial, a single subacromial injection of tenoxicam was not as effective as methylprednisolone; the idea of using subacromial injection of NSAIDs is attractive. In the UK over half a million intra-articular glucocorticoid injections are administered per year in the primary care setting alone but there is very little information on how glucocorticoids may affect rotator cuff tendons *in vivo*<sup>368</sup>. Emerging clinical evidence shows significant long-term harm to tendon tissue and cells associated with local glucocorticoid injections including reduced cell viability, cell proliferation, collagen synthesis and increased collagen disorganisation and necrosis<sup>368,369</sup>.

Extensive research is being carried out to find an effective alternative for corticosteroid injection. A recent double blind RCT comparing a subacromial injection of ketorolac resulted in greater improvements in the UCLA shoulder rating scale than an injection of triamcinolone at 4 weeks' follow-up<sup>370</sup>. This may lead to further studies with different NSAID preparations, dosage and frequency of administration. It is worth noting that all these studies have had only a short follow-up period of 4 to 6 weeks but determining the long-term effects of subacromial injection, although desirable should come after the first step which is to establish if treatments have any effect in the short to medium term.

Other studies included subacromial platelet rich plasma (PRP) injections with variable results<sup>371,372</sup>. Scarpone et al found that a single injection of PRP resulted in significant improvement of pain and function<sup>372</sup> but Kesikburun et al found PRP injection to be no more effective than placebo<sup>371</sup>. A review of trial registries reveals researchers embarking on some unconventional interventions. A research group in London are carrying out a randomised single blinded placebo controlled study investigating the role of poly-unsaturated fatty acids in addition to exercise in the management of rotator cuff tendinopathy (ISRCTN17856844). While in Europe, researchers are comparing an intra-articular injection of corticosteroid with hyaluronic acid in the treatment of rotator cuff tendinopathy (EU clinical trials register; EudraCT Number: 2011-003207-37). The fact that different drugs are still being trialled for such a common condition is probably an indication that no drug is consistently effective or without adverse effects.

Research trials are not confined to just non-operative management of rotator cuff pathology. When conservative management fails, surgery is an option for treating subacromial impingement. This can involve an Arthroscopic Subacromial Decompression (ASAD), an operation to remove the bony spurs from the under-surface of the acromion, which may be the cause for the pain. Can Shoulder Arthroscopy Work (CSAW)<sup>373</sup> is a randomised controlled trial that will compare ASAD against an investigational shoulder arthroscopy (without spur removal/decompression) to indicate whether spur removal is really necessary. Both treatments will be compared against a control (non-operative management with specialist reassessment) group to indicate whether surgery in general is effective for patients with subacromial pain. Patients randomised to

either of the surgical options will be blinded to the type of surgery they have. The study plans to recruit 300 men and women with sub-acromial shoulder pain and complete by April 2017.

Likewise, the UK Rotator Cuff Surgery (UKUFF)<sup>374</sup> is a pragmatic multicenter randomised controlled trial (RCT) to assess the clinical and cost effectiveness of arthroscopic and open surgery in the management of rotator cuff tears. Of note is that nearly 20% of patients in the trial underwent subacromial decompression and not cuff repair. This was due to either no tear being found or the tear was found to be too large to repair, despite using MRI or ultrasound to diagnose full thickness rotator cuff tears to determine participation in the study. At 12 months, re-tears were found in 40% of patients who underwent repair surgery, with no relation to age or the tear size. Future work should explore new methods to improve tendon healing and reduce the high rate of re-tears observed in this trial.

The observational study on the normal ultrasound anatomy of rotator cuff is a start at the documentation of normal shoulder anatomy and establishing normal reference values. All measurements in the study were made in asymptomatic volunteers under the age of forty years. The likelihood of significant rotator cuff pathology is minimal in this age group. The incidence of rotator cuff pathology increases with age. The rotator cuff muscle dimensions are likely to be different in other age categories. Further studies should be done to look at the normal dimensions in other age groups, for example 41-60, 61-70, and 71-80 years to

document the reference values in those age groups most likely to have pathology.

The pathogenesis of rotator cuff disease is complex, multifactorial and not fully understood still. Many researchers have investigated the microvascular blood flow in the supraspinatus tendon in an attempt to find why most of the rotator cuff tears occur at a point just proximal to its insertion into the humerus. Recent *in vivo* studies using percutaneous biopsies of supraspinatus tendons with full thickness tears undergoing rotator cuff repair have shown poor vascularity on histology<sup>368</sup>. Researchers have proposed that the position of arm may be a contributing factor for the presence of a critical zone of hypoperfusion. Although our study did not find an avascular or hypovascular zone in patients with a normal rotator cuff, all our measurements were taken in the shoulder with the arm by the side of the body. Future studies may address this by taking measurements with the arm in different positions. In our study, we were unable to age match the different pathological groups with the normal rotator cuff group. Degenerative nature of rotator cuff pathology meant that the pathological groups were older and due to the interventional nature of the study, the group for normal rotator cuff consisted of individuals who had arthroscopic shoulder surgery for non-cuff related pathology. These individuals turned out to be predominantly men and much younger. Prospective studies in the future should try and age match the different groups, but ethical considerations mean that this may not always be possible.

To conclude, this thesis has demonstrated that subacromial injection of a corticosteroid is more effective than a NSAID in the short-term management of subacromial impingement. It has documented the dimensions of normal rotator cuff using ultrasound and has shown that the asymptomatic contralateral shoulder in everyone can be used as a control. This thesis has shown that microvascular blood flow in the normal rotator cuff is not uniform but there is no evidence of a “critical zone” of hypoperfusion using a laser Doppler probe, a modern, in-vivo, real-time, physiologic technique. This body of work has contributed to our growing understanding of the pathogenesis, diagnosis and treatment of rotator cuff pathology.

Appendix A: Comparison of ultrasonographic findings with arthroscopy.

# Imaging of rotator cuff Is ultrasonography reliable?

S Karthikeyan; S Rai and S Drew.

## INTRODUCTION

In patients with shoulder pain one of the important initial determinations is to assess the integrity of the rotator cuff. Clinical examination is often inconclusive. Diagnostic imaging is necessary to plan treatment and determine prognosis.

MRI, Arthrography and Ultrasound have been used to assess rotator cuff. Compared with MRI and arthrography, ultrasound allows dynamic evaluation, is non-invasive, less expensive, less time consuming and more acceptable to patients.

However in studies comparing US findings with surgery the sensitivity for detecting rotator cuff tears have varied between 57% and 100% and specificity between 50% and 98%. The aim of the present study was to evaluate the accuracy of high resolution shoulder ultrasonography compared with arthroscopy in a series of consecutive patients with clinically suspected rotator cuff disease.

## MATERIALS & METHODS

100 shoulders in 99 consecutive patients with shoulder pain who had undergone standardized preoperative ultrasonography and subsequent arthroscopy between May 2004 and March 2006 were included in the study. There were 53 males and 46 females with a mean age of 59 years (range 26-82 years). The mean time interval between the ultrasonographic and the arthroscopic examination was 227 days (range 15-678 days).

Surgery was considered in patients with shoulder pain of more than six months duration who did not respond to nonoperative treatment consisting of physical therapy, nonsteroidal anti-inflammatory medications and at least one subacromial corticosteroid injection.

## Ultrasonographic technique

All ultrasonographic examinations were performed by a single experienced musculoskeletal radiologist using an ATL Ultramark HDI 5000 scanner with a 5-12MHz linear array probe.

The examination was performed with the patient seated on a stool and the radiologist seated facing the patient. All tendons were imaged in the transverse and longitudinal planes. The long head of biceps tendon was imaged first, in the Intertubercular groove, with the patient's hand resting on their thigh with the thumb pointing towards the ceiling. The shoulder was then externally rotated and the subscapularis tendon was visualised. Dynamic studies were obtained by alternating between external rotation and a neutral position. The patient was then asked to internally rotate the shoulder by placing the hand behind their back as if reaching for a wallet in a trouser pocket. The supraspinatus tendon was then visualised. The examination was concluded by asking the patient to place their hand on the opposite shoulder allowing the infraspinatus tendon to be viewed.

## Ultrasonographic criteria

A full thickness rotator cuff tear was diagnosed when the cuff could not be visualized because of complete avulsion and retraction under the acromion or when there was a focal defect in the cuff created by a variable degree of retraction of the torn tendon ends.

A partial-thickness tear was diagnosed when there was a defect on the bursal side of the cuff or a distinct hypo echoic or mixed hyper echoic and hypo echoic defect on the articular side of the cuff.

## Surgical technique

All arthroscopic procedures were done by or under the supervision of a single orthopaedic surgeon.

Patient was placed in the beach-chair position under general anaesthesia. Arthroscope was introduced posteriorly and an anterior portal used for instrumentation.

The presence or absence of a full thickness tear or of a bursal or articular side partial thickness tear was recorded. Representative arthroscopic images were made of all tears.

## RESULTS

Ultrasonography correctly identified all 40 full thickness tears that were diagnosed on arthroscopy. Ultrasonography incorrectly identified full thickness tears in 10 other shoulders that were found to have a partial thickness tear on arthroscopy. There were no false negative results. Ultrasonography showed a sensitivity of 100% (40 of 40) in detecting full thickness tears, specificity 83% (50 of 60), positive predictive value 80% (40 of 50), negative predictive value 100% (50 of 50) and accuracy 90% (90 of 100).

Ultrasonography correctly identified 14 of the 29 partial thickness tears diagnosed on arthroscopy. A full thickness rather than a partial thickness tear was identified in 10 shoulders. Because a tear was identified these studies were considered to be true positive. There were 5 false negative and 4 false positive studies. Ultrasonography showed a sensitivity of 83% (24 of 29) in detecting partial thickness tears, specificity 94% (67 of 71), positive predictive value 86% (24 of 28), negative predictive value 93% (67 of 72) and accuracy 91% (91 of 100).

Ultrasonography correctly predicted the absence of a tear in 27 of the 31 shoulders that had no evidence of a tear on arthroscopy.

Ultrasonography	Arthroscopy			Total
	FTT	PTT	Negative	
FTT	40	10	0	50
PTT	0	14	4	18
Negative	0	5	27	32
Total	40	29	31	100

Table 1

## DISCUSSION

The use of high resolution shoulder ultrasonography to diagnose rotator cuff tears has achieved only limited acceptance by the orthopaedic surgeons. This may be due in part to the lack of local radiological expertise, difficulty in recognizing the relevant anatomy and pathology on hand copy ultrasound images and uncertainty about the true accuracy of this modality.

Refinements in scanning technique, modern equipment with improved resolution capabilities and clarification of criteria for diagnosing rotator cuff tears have improved the accuracy of shoulder ultrasonography.

## CONCLUSION

In our experience ultrasonography is found to be a highly accurate and reliable technique for detecting rotator cuff tears. Our results are comparable with MRI in terms of accuracy for detecting FT tears.

Ultrasonography offers other advantages as it provides bilateral information, is better tolerated, allows patient to view real time information and is less expensive. However the success of an ultrasonographic examination is heavily dependent on the experience of the operator.



Fig 1 Normal supraspinatus



Fig 2 Normal supraspinatus



Fig 3 Partial thickness tear



Fig 4 Articular sided partial thickness tear



Fig 5 Full thickness tear



Fig 6 Full thickness tear

## CONTACT

s.karthikeyan@warwickorthopaedics.com

## Appendix B: Constant Shoulder Score

Name _____		Date _____		Age _____		Insurance _____																																			
Handedness: R L B				Side: R L																																					
Operation / Diagnosis _____																																									
Examination: Pre-op 3 Months 6 Months 1 Year 2 years ___years																																									
<b>Pain (15 Points): (Average of 1+2)</b>							<b>A</b>																																		
1. Do you have pain in your shoulder during normal activities? No=15 Mild=10 Moderate=5 Severe or permanent=0																																									
2. If "0" means no pain and "15" is the maximum pain you can experience, please circle the level of pain you experience in your shoulder in general.																																									
<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="text-align: left;"><b>Level of Pain</b></td> <td><b>0</b></td><td><b>1</b></td><td><b>2</b></td><td><b>3</b></td><td><b>4</b></td><td><b>5</b></td><td><b>6</b></td><td><b>7</b></td><td><b>8</b></td><td><b>9</b></td><td><b>10</b></td><td><b>11</b></td><td><b>12</b></td><td><b>13</b></td><td><b>14</b></td><td><b>15</b></td> </tr> <tr> <td style="text-align: left;">Points</td> <td>15</td><td>14</td><td>13</td><td>12</td><td>11</td><td>10</td><td>9</td><td>8</td><td>7</td><td>6</td><td>5</td><td>4</td><td>3</td><td>2</td><td>1</td><td>0</td> </tr> </table>								<b>Level of Pain</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>13</b>	<b>14</b>	<b>15</b>	Points	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1	0
<b>Level of Pain</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>13</b>	<b>14</b>	<b>15</b>																									
Points	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1	0																									
<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 10%;"></td> </tr> </table>																																									
<b>Activities of Daily Living (20 points): Total (1+2+3+4)</b>							<b>B</b>																																		
1. Is your occupation or daily living limited by your shoulder? No=4 Moderate limitation=2 Severe limitation=0																																									
2. Are your leisure and recreational activities limited by your shoulder? No=4 Moderate limitation=2 Severe limitation=0																																									
3. Is your night sleep disturbed by your shoulder? No=4 Moderate limitation=2 Severe limitation=0																																									
4. State to what level you can use your arm for painless work-related or daily activities. Waist=2 Xiphoid (sternum)=4 Neck=6 Head=8 Above head=10																																									
<b>Range of Motion (leave this to the doctor or physical therapist)/(40 points): Total (1+2+3+4)</b>							<b>C</b>																																		
<b>1. Forward flexion</b>		<b>2. Abduction</b>		<b>3. External Rotation</b>		<b>4. Internal Rotation</b>																																			
0-30	0	0-30	0	Hand behind head & elbow forward	2	Dorsum of hand to....																																			
31-60	2	31-60	2	Hand behind head & elbow back	4	Lateral thigh	0																																		
61-90	4	61-90	4	Hand above head & elbow forward	6	Buttock	2																																		
91-120	6	91-120	6	Hand above head & elbow back	8	LS junction	4																																		
121-150	8	121-150	8	Full elevation of arm	10	Waist (L3)	6																																		
>150	10	>150	10			T12	8																																		
						Interscapular area T7	10																																		
<b>Strength of Abduction (25 points): Average (kg) (To 90 degrees abduction or highest level patient can achieve)</b>																																									
Trial 1 _____		Trail 2 _____		Trial 3 _____		Average _____																																			
							<b>D</b>																																		
<b>Total Constant Score: A+B+C+D</b>																																									

## Appendix C: DASH Score

### DISABILITIES OF THE ARM, SHOULDER AND HAND

THE

# DASH

#### INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to perform certain activities.

Please answer *every question*, based on your condition in the last week, by circling the appropriate number.

If you did not have the opportunity to perform an activity in the past week, please make your *best estimate* on which response would be the most accurate.

It doesn't matter which hand or arm you use to perform the activity; please answer based on your ability regardless of how you perform the task.



## DISABILITIES OF THE ARM, SHOULDER AND HAND

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Write.	1	2	3	4	5
3. Turn a key.	1	2	3	4	5
4. Prepare a meal.	1	2	3	4	5
5. Push open a heavy door.	1	2	3	4	5
6. Place an object on a shelf above your head.	1	2	3	4	5
7. Do heavy household chores (e.g., wash walls, wash floors).	1	2	3	4	5
8. Garden or do yard work.	1	2	3	4	5
9. Make a bed.	1	2	3	4	5
10. Carry a shopping bag or briefcase.	1	2	3	4	5
11. Carry a heavy object (over 10 lbs).	1	2	3	4	5
12. Change a lightbulb overhead.	1	2	3	4	5
13. Wash or blow dry your hair.	1	2	3	4	5
14. Wash your back.	1	2	3	4	5
15. Put on a pullover sweater.	1	2	3	4	5
16. Use a knife to cut food.	1	2	3	4	5
17. Recreational activities which require little effort (e.g., cardplaying, knitting, etc.).	1	2	3	4	5
18. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5
19. Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	1	2	3	4	5
20. Manage transportation needs (getting from one place to another).	1	2	3	4	5
21. Sexual activities.	1	2	3	4	5

## DISABILITIES OF THE ARM, SHOULDER AND HAND

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
22. During the past week, <i>to what extent</i> has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? <i>(circle number)</i>	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
23. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? <i>(circle number)</i>	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*

	NONE	MILD	MODERATE	SEVERE	EXTREME
24. Arm, shoulder or hand pain.	1	2	3	4	5
25. Arm, shoulder or hand pain when you performed any specific activity.	1	2	3	4	5
26. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5
27. Weakness in your arm, shoulder or hand.	1	2	3	4	5
28. Stiffness in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? <i>(circle number)</i>	1	2	3	4	5

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem. <i>(circle number)</i>	1	2	3	4	5

**DASH DISABILITY/SYMPTOM SCORE** =  $\frac{(\text{sum of } n \text{ responses})}{n} - 1$  x 25, where n is equal to the number of completed responses.

A DASH score may not be calculated if there are greater than 3 missing items.

## DISABILITIES OF THE ARM, SHOULDER AND HAND

### WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including home-making if that is your main work role).

Please indicate what your job/work is: \_\_\_\_\_

I do not work. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for your work?	1	2	3	4	5
2. doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. doing your work as well as you would like?	1	2	3	4	5
4. spending your usual amount of time doing your work?	1	2	3	4	5

### SPORTS/PERFORMING ARTS MODULE (OPTIONAL)

The following questions relate to the impact of your arm, shoulder or hand problem on playing *your musical instrument or sport or both*. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you: \_\_\_\_\_

I do not play a sport or an instrument. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for playing your instrument or sport?	1	2	3	4	5
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. playing your musical instrument or sport as well as you would like?	1	2	3	4	5
4. spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

**SCORING THE OPTIONAL MODULES:** Add up assigned values for each response; divide by 4 (number of items); subtract 1; multiply by 25.

An optional module score may **not** be calculated if there are any missing items.

## Appendix D: Oxford Shoulder Score

Shoulder Surgery Questionnaire – Before / after your operation

### PROBLEMS WITH YOUR SHOULDER

Tick (✓) one box for every question.

<b>1. During the past 4 weeks...</b>				
How would you describe the <b>worst</b> pain you had <u>from your shoulder</u> ?				
None	Mild	Moderate	Severe	Unbearable
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>2. During the past 4 weeks...</b>				
Have you had any trouble dressing yourself <u>because of your shoulder</u> ?				
No trouble at all	A little bit of trouble	Moderate trouble	Extreme difficulty	Impossible to do
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>3. During the past 4 weeks...</b>				
Have you had any trouble getting in and out of a car or using public transport <u>because of your shoulder</u> ?				
No trouble at all	A little bit of trouble	Moderate trouble	Extreme difficulty	Impossible to do
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>4. During the past 4 weeks...</b>				
Have you been able to use a knife and fork - <u>at the same time</u> ?				
Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>5. During the past 4 weeks...</b>				
Could you do the household shopping <u>on your own</u> ?				
Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>6. During the past 4 weeks...</b>				
Could you carry a tray containing a plate of food across a room?				
Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**7. During the past 4 weeks...**

Could you brush/comb your hair with the affected arm?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**8. During the past 4 weeks...**

How would you describe the pain you usually had from your shoulder?

None	Very mild	Mild	Moderate	Severe
<input type="checkbox"/>				

**9. During the past 4 weeks...**

Could you hang your clothes up in a wardrobe, using the affected arm?

Yes, easily	With little difficulty	With moderate difficulty	With great difficulty	No, impossible
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**10. During the past 4 weeks...**

Have you been able to wash and dry yourself under both arms?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**11. During the past 4 weeks...**

How much has pain from your shoulder interfered with your usual work (including housework)?

Not at all	A little bit	Moderately	Greatly	Totally
<input type="checkbox"/>				

**12. During the past 4 weeks...**

Have you been troubled by pain from your shoulder in bed at night?

No nights	Only 1 or 2 nights	Some nights	Most nights	Every night
<input type="checkbox"/>				

**Finally, please check back that you have answered each question.  
Thank you very much.**

## **Appendix E: BREC approval for ultrasound study**

22 February 2010

Chris Smith  
Clinical lecturer in Trauma and Orthopaedic Surgery  
Clinical Sciences Research Institute  
Warwick Medical School  
Clifford Bridge Road  
Walsgrave  
Coventry  
CV2 2DX

Dear Chris

Project Title: The normal ultrasound dimensions of the rotator cuff in young (18-40yrs) healthy asymptomatic volunteers.

---

Thank you for submitting your revisions for the above-named project to the University of Warwick Biomedical Research Ethics Sub-Committee for Chair's Approval.

The Chair is pleased to confirm that the revised documentation meets the required standard which means that full approval is granted and your study may commence. May I remind you any substantial amendments require approval from the Committee and that, once your study is completed, the Committee would welcome an End of Project Report.

Yours sincerely,

Professor Jane Barlow  
Chair  
Biomedical Research  
Ethics Sub-Committee

Copy:  
Lynn Green, Research Governance Facilitator, WMS

**The normal ultrasound dimensions of the rotator cuff in young (18-40yrs) healthy asymptomatic volunteers.**

**Are you between 18yr and 40yrs of age?**

**Are you fit and healthy?**

**If yes, would you consider volunteering to undergo an ultrasound scan of your shoulders?**

**We are performing a study to determine the normal ultrasound dimensions of the rotator cuff muscle (inner muscle of the shoulder). If you are between 18and 40yrs of age, are fit and healthy and have never had a problem with your shoulders, you may be suitable as a volunteer.**

**The ultrasound assessment is a non-invasive procedure. It requires the exposure of the shoulder only, application of ultrasound jelly and an ultrasound examination. This will take no longer than ten minutes in total and will be performed in a warm private consultation room. There are no known disadvantages or risks associated with ultrasound.**

**If you would like further information about volunteering or to be considered for the study please contact Mr Chris Smith, who is leading the study either by email or phone.**

Telephone: 02476 968628

Email: christopher.d.smith@warwick.ac.uk.

## **Appendix G:** Information sheet for ultrasound study

### **Participation Information Sheet**

#### **The normal ultrasound dimensions of the rotator cuff in young (18yrs-40yrs) healthy asymptomatic volunteers.**

*Chief Investigator: Mr Chris Smith*

#### **Background Information**

The inner muscle of the shoulder is called the rotator cuff. Tears of the rotator cuff of the shoulder are a serious and disabling condition. The condition can affect adult patients of all ages and is associated with prolonged periods off work and much longer abstinence from sporting activities. The diagnosis of these tears is commonly made by ultrasound. The diagnosis of partial tears relies on assessing the thickness of the muscle. However, the dimensions of the rotator cuff in the normal healthy population have not been previously presented, specifically relating to hand dominance and gender. This information is important to document and use as a reference to guide surgeons when reviewing ultrasound scans.

#### **What is the purpose of the study?**

To assess the dimensions of the rotator cuff in the normal young (<40yrs old) healthy volunteer.

#### **Why have I been approached?**

As you are a healthy young volunteer with no previous shoulder problems or surgery. A total of 60 volunteers will be recruited.

#### **What will happen after I have been entered in the study?**

You will undergo a non-invasive ultrasound scan of each shoulder. This requires the exposure of the shoulder only, application of ultrasound jelly and an ultrasound examination. This will take no longer than ten minutes in total.

#### **Do I have to take part?**

It is up to you whether or not to take part.

#### **What are the possible disadvantages and risks of taking part?**

There are no known disadvantages or risks associated with ultrasound.

#### **What are the possible benefits to you of taking part?**

There is no specific benefit to you for taking part in the study. However, the information obtained from this study may help us to treat future patients with damage to the rotator cuff.

#### **What happens if an abnormality is detected?**

This is unlikely as you do not have any problems with your shoulders. However, if any abnormality is identified you will be informed at the time of the scan and a referral to a shoulder surgeon can be made.

**Will my taking part in this study be kept confidential?**

All information which is collected about you during the course of the research will be strictly confidential.

**What will happen to the results of the research study?**

At the end of the study the results will be published in medical journals and at medical conferences. You will not be identified in any reports or publications resulting from the study.

**Who has reviewed this study?**

This study has been reviewed by Warwick University's Biomedical Research Ethics Committee.

**Contacts for further information**

If you would like further information please contact Karthik on 02476 968622 or emailing [shanmugam.karthikeyan@warwick.ac.uk](mailto:shanmugam.karthikeyan@warwick.ac.uk). Alternatively you can contact Mr Chris Smith who is leading the project by emailing [christopher.d.smith@warwick.ac.uk](mailto:christopher.d.smith@warwick.ac.uk).

## Appendix H: Consent for ultrasound study

### Volunteer consent form for shoulder ultrasound assessment of the young health adult

Study ID:		Date (dd/mm/yy):	
Name of Volunteer:		D.O.B (dd/mm/yy):	

Chief Investigator

Mr Chris Smith

Please initial box

1. I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason.

3. I agree to take part in the above study.

\_\_\_\_\_  
Name of Volunteer

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Chris Smith (Chief Investigator)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

## Appendix I: Research Ethics Committee favourable decision letter



### Coventry & Warwickshire Research Ethics Committee

Prospect House  
Fishing Line Road  
Enfield  
Redditch  
B97 6EW

Telephone: 01527 582531  
Facsimile:

03 November 2010

Mr Christopher D Smith  
Clinical lecturer in Trauma and Orthopaedic Surgery  
University of Warwick  
CSRI, Warwick Medical School  
Clifford Bridge Road  
Coventry  
CV2 2DX

Dear Mr Smith

**Study Title:** What is the microvascular blood flow in the normal and pathological rotator cuff?  
**REC reference number:** 10/H1211/42

The Research Ethics Committee reviewed the above application at the meeting held on 27 October 2010. The Committee would like to thank Mr Karthikeyan Shanmugan for attending to discuss the application.

#### Discussion

- The Committee congratulated the researcher on producing a well thought out project.
- It is not clear in the Participant Information Sheet who will be the independent contact point for potential participants and the Committee suggested that the PALS office is used and Mr Shanmugan agreed to address this.

#### **Decision: Favourable Opinion with conditions**

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

#### **Ethical review of research sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

#### **Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

- ***The Participant Information Sheet should include an independent contact for potential participants and the Committee suggested that the PALS office is used.***

**Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.**

Management permission ["R & D approval] should be sought from all NHS organisations[s] involved in the study in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System [IRAS] or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ["participant identification centre"], guidance should be sought from the R & D Office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

*Sponsors are not required to notify the Committee of approvals from host organisations.*

**It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers.**

**Contact for further information**

If you require any further information please contact Mrs Anne McCullough, our co-ordinator, in the first instance.

**Approved documents**

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Investigator CV		30 September 2010
Protocol	v2	11 September 2010
CV - Key Collaborator		30 September 2010
REC application		24 September 2010
Participant Information Sheet: PIS	v2	11 September 2010
Participant Consent Form: Consent Form	v2	11 September 2010
CV - Key Collaborator		30 September 2010
Evidence of insurance or indemnity		03 August 2010

**Membership of the Committee**

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

### After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

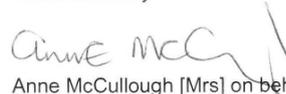
We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email [referencegroup@nres.npsa.nhs.uk](mailto:referencegroup@nres.npsa.nhs.uk).

**10/H1211/42**

**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely



Anne McCullough [Mrs] on behalf of  
**Dr Helen Brittain**  
**Chair**

Email: [anne.mccullough@westmidlands.nhs.uk](mailto:anne.mccullough@westmidlands.nhs.uk)

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments "After ethical review – guidance for researchers"*

Copy to: *Dr Peter Hedges*

**Appendix J: Sponsorship agreement between University of Warwick and UHCW NHS Trust**

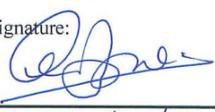
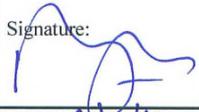
**Appendix B**

**Sponsorship Agreement for microvascular blood flow in rotator cuff**

*Nomination of Sponsor & Allocation of Responsibilities under the Research Governance Framework*

Full title of research project	What is the microvascular blood flow in the normal and pathological rotator cuff?
Short Title	Blood flow in pathological rotator cuff
EudraCT Number	N/A
CTX/DDX/CTA Number	R&D ref: CS068409
Funder	Academy of Medical Sciences and Wellcome Trust
Contract Administered at	University of Warwick
Collaborating organisations involved in research project	1. University of Warwick: Mr Christopher Smith, Prof Griffin. 2. UHCW NHS Trust: Mr Steve Drew, Mr Shanmugam Karthikeyan.
Name of Chief Investigator	Mr Christopher Smith
Employing Organisation of Chief Investigator	University of Warwick (UoW)

The parties outlined below agree the nomination of sponsor and delegation of duties for this research project only as outlined on this form

<i>Sponsor 1</i>	<i>Sponsor 2</i>
University Hospitals Coventry & Warwickshire NHS Trust (UHCW)	University of Warwick (UoW)
Authorised Name: Mrs Ceri Jones, Research & Development Services Manager	Authorised Name: Mr Peter Hedges Director of Research Support Services
Signature: 	Signature: 
Date: 22/10/10	Date: 20/10/10

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Final Research Governance Agreement between Co-Sponsors – each collaborating centre will be required to sign up to the responsibilities as detailed in this agreement.

## Appendix K: Patient information sheet for microvascular blood flow study

### ***Participant Information Sheet for blood flow within the rotator cuff study***

---

Chief Investigator                      Mr Chris Smith

#### **Background Information**

The inner muscle of the shoulder is called the rotator cuff. Tears of the rotator cuff of the shoulder are a serious and disabling condition. The condition can affect adult patients of all ages and is associated with prolonged periods off work and much longer abstinence from sporting activities. One treatment for these tears is keyhole surgery. The ability of these tears to heal is thought to be related to how much blood flow there is within the rotator cuff. This is presently not known. By recording this in a variety of patients it is hoped that this may guide surgeons to understand which tears will heal after repair and which will not.

#### **What is the purpose of the study?**

We are assessing the blood flow within the rotator cuff in patients undergoing keyhole shoulder surgery. This data is important to inform and lead developments in the treatment of rotator cuff tears.

#### **Why have I been chosen?**

All patients under the care of Mr Steve Drew attending this hospital for keyhole shoulder surgery will be invited to take part in this study. A total of 120 patients will be recruited.

#### **What will happen after I have been entered in the study?**

Standard Practice: You will undergo keyhole surgery for assessment and treatment of your shoulder condition.

Research Practice (If you take part in the study): You will undergo a series of measurements using a small probe placed into the shoulder through one of the standard keyholes already made for the arthroscopic (keyhole) procedure. This additional measurement will add about five minutes to the length of the operation and will not influence or affect the surgery performed.

**Do I have to take part?**

It is up to you whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. A decision not to take part will not affect the standard of care you receive; you will receive the same normal care as someone not invited to take part in the experiment.

**What are the possible disadvantages and risks of taking part?**

There are no known disadvantages to taking part in the study because your treatment will not change.

**What are the possible benefits to you of taking part?**

There is no specific benefit to you for taking part in the study. However, the information we get from this study may help us to treat future patients with damage to the rotator cuff.

**What happens if something goes wrong?**

In the unlikely event of you being harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you may contact Mrs Ceri Jones, R&D services manager at the University Hospital on 02476 96196 or [Mrs Nicola Owen, deputy registrar at the University of Warwick on 02476 522785](#)

**Will my taking part in this study be kept confidential?**

All information which is collected about you during the course of the research will be strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

**What will happen to the results of the research study?**

At the end of the study we will publish the findings in medical journals and at medical conferences. You will not be identified in any reports or publications resulting from the

study. If you would like to obtain a copy of the published results, please contact Professor Damian Griffin's secretary (02476-968618).

**What will happen if I decide not to participate in the research study?**

There will be no change to your treatment.

**Who has reviewed this study?**

This study has been reviewed by Coventry and Warwickshire Research Ethics Committee.

**Contacts for further information**

If you would like further information please contact Mr S Karthikeyan (Karthik) who is organising the project by telephoning 02476 968622 or emailing [shanmugam.karthikeyan@warwick.ac.uk](mailto:shanmugam.karthikeyan@warwick.ac.uk)

For independent advice about taking part in research, potential participants can contact the Patient Advice Liaison Service (PALS) on telephone number 0800 028 4203 or by email [PALS@uhcw.nhs.uk](mailto:PALS@uhcw.nhs.uk)

## Appendix L: Patient consent form

### *Patient Consent form for blood flow within the rotator cuff study*

Trial Centre ID:		Date (dd/mm/yy):	
Name of Patient:		D.O.B (dd/mm/yy):	

Chief Investigator

Mr Chris Smith

Please initial box

1. I confirm that I have read and understand the patient information sheet dated 20-11-2010 (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities, the University of Warwick or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

\_\_\_\_\_  
Name of Patient

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

*S Karthikeyan*

\_\_\_\_\_  
Name of Person taking consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

*Research Fellow*

\_\_\_\_\_  
Role of Person taking consent

## References

1. **Picavet HS, Schouten JS.** Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. *Pain* 2003;102-1-2:167-78.
2. **Macfarlane GJ, Hunt IM, Silman AJ.** Predictors of chronic shoulder pain: a population based prospective study. *J Rheumatol* 1998;25-8:1612-5.
3. **Practitioners. RCoG.** Morbidity statistics from general practice. Third national study:socio-economic analyses. In: Office of Population Census and Surveys DoHaSS, ed. London: HMSO, 1986.
4. **Mitchell C, Adebajo A, Hay E, Carr A.** Shoulder pain: diagnosis and management in primary care. *BMJ* 2005;331-7525:1124-8.
5. **Urwin M, Symmons D, Allison T, Brammah T, Busby H, Roxby M, Simmons A, Williams G.** Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. *Ann Rheum Dis* 1998;57-11:649-55.
6. **Chard MD, Hazleman R, Hazleman BL, King RH, Reiss BB.** Shoulder disorders in the elderly: a community survey. *Arthritis Rheum* 1991;34-6:766-9.
7. **Ostor AJ, Richards CA, Prevost AT, Hazleman BL, Speed CA.** Interrater reproducibility of clinical tests for rotator cuff lesions. *Ann Rheum Dis* 2004;63-10:1288-92.
8. **Rechardt M, Shiri R, Karppinen J, Jula A, Heliovaara M, Viikari-Juntura E.** Lifestyle and metabolic factors in relation to shoulder pain and rotator cuff tendinitis: a population-based study. *BMC Musculoskelet Disord* 2010;11:165.
9. **Neer CS, 2nd.** Impingement lesions. *Clin Orthop Relat Res* 1983-173:70-7.
10. **Li XX, Schweitzer ME, Bifano JA, Lerman J, Manton GL, El-Noueam KI.** MR evaluation of subscapularis tears. *J Comput Assist Tomogr* 1999;23-5:713-7.
11. **O'Brien SJ, Voos JE, Neviasser AS, Drakos MC.** Developmental anatomy of the shoulder and anatomy of the glenohumeral joint. In: Rockwood CA, Matsen FA, eds. *The shoulder*. Vol. 1, 4th edition ed. Philadelphia: Elsevier Health Sciences, 2009:8.
12. **Clark JM, Harryman DT, 2nd.** Tendons, ligaments, and capsule of the rotator cuff. Gross and microscopic anatomy. *J Bone Joint Surg Am* 1992;74-5:713-25.
13. **DeFranco MJ, Cole BJ.** Current perspectives on rotator cuff anatomy. *Arthroscopy* 2009;25-3:305-20.
14. **Minagawa H, Itoi E, Konno N, Kido T, Sano A, Urayama M, Sato K.** Humeral attachment of the supraspinatus and infraspinatus tendons: an anatomic study. *Arthroscopy* 1998;14-3:302-6.

15. Roh MS, Wang VM, April EW, Pollock RG, Bigliani LU, Flatow EL. Anterior and posterior musculotendinous anatomy of the supraspinatus. *J Shoulder Elbow Surg* 2000;9-5:436-40.
16. Clark J, Sidles JA, Matsen FA. The relationship of the glenohumeral joint capsule to the rotator cuff. *Clin Orthop Relat Res* 1990-254:29-34.
17. Chansky HA, Iannotti JP. The vascularity of the rotator cuff. *Clin Sports Med* 1991;10-4:807-22.
18. Ling SC, Chen CF, Wan RX. A study on the vascular supply of the supraspinatus tendon. *Surg Radiol Anat* 1990;12-3:161-5.
19. Determe D, Rongieres M, Kany J, Glasson JM, Bellumore Y, Mansat M, Becue J. Anatomic study of the tendinous rotator cuff of the shoulder. *Surg Radiol Anat* 1996;18-3:195-200.
20. Hegedus EJ, Cook C, Brennan M, Wyland D, Garrison JC, Driesner D. Vascularity and tendon pathology in the rotator cuff: a review of literature and implications for rehabilitation and surgery. *Br J Sports Med* 2010;44-12:838-47.
21. Lohr JF, Uhthoff HK. The microvascular pattern of the supraspinatus tendon. *Clin Orthop Relat Res* 1990-254:35-8.
22. Rothman RH, Parke WW. The vascular anatomy of the rotator cuff. *Clin Orthop Relat Res* 1965;41:176-86.
23. Rathbun JB, Macnab I. The microvascular pattern of the rotator cuff. *J Bone Joint Surg Br* 1970;52-3:540-53.
24. Moseley HF, Goldie I. The Arterial Pattern of the Rotator Cuff of the Shoulder. *J Bone Joint Surg Br* 1963;45:780-9.
25. Levy O, Relwani J, Zaman T, Even T, Venkateswaran B, Copeland S. Measurement of blood flow in the rotator cuff using laser Doppler flowmetry. *J Bone Joint Surg Br* 2008;90-7:893-8.
26. Silvestri E, Biggi E, Molfetta L, Avanzino C, La Paglia E, Garlaschi G. Power Doppler analysis of tendon vascularization. *Int J Tissue React* 2003;25-4:149-58.
27. Swiontkowski MF, Iannotti JP, Boulas HJ, Esterhai JL. Intraoperative assessment of rotator cuff vascularity using laser Doppler flowmetry. In: Post M, Morrey BF, eds. *Surgery of the shoulder*. St. Louis: Mosby, 1990.
28. Codman E. *The shoulder: rupture of the supraspinatus tendon and other lesions in or about the subacromial bursa*. Boston: Thomas Todd, 1934.
29. Killian ML, Cavinatto L, Galatz LM, Thomopoulos S. The role of mechanobiology in tendon healing. *J Shoulder Elbow Surg* 2012;21-2:228-37.
30. Abate M, Silbernagel KG, Siljeholm C, Di Iorio A, De Amicis D, Salini V, Werner S, Paganelli R. Pathogenesis of tendinopathies: inflammation or degeneration? *Arthritis Res Ther* 2009;11-3:235.
31. Sharma P, Maffulli N. Basic biology of tendon injury and healing. *Surgeon* 2005;3-5:309-16.

- 32. Vailas AC, Tipton CM, Laughlin HL, Tcheng TK, Matthes RD.** Physical activity and hypophysectomy on the aerobic capacity of ligaments and tendons. *J Appl Physiol Respir Environ Exerc Physiol* 1978;44-4:542-6.
- 33. Franchi M, Trire A, Quaranta M, Orsini E, Ottani V.** Collagen structure of tendon relates to function. *ScientificWorldJournal* 2007;7:404-20.
- 34. Reeves ND.** Adaptation of the tendon to mechanical usage. *J Musculoskelet Neuronal Interact* 2006;6-2:174-80.
- 35. Carr AJ, Norris SH.** The blood supply of the calcaneal tendon. *J Bone Joint Surg Br* 1989;71-1:100-1.
- 36. Armenta E, Lehrman A.** The vincula to the flexor tendons of the hand. *J Hand Surg Am* 1980;5-2:127-34.
- 37. Leversedge FJ, Ditsios K, Goldfarb CA, Silva MJ, Gelberman RH, Boyer MI.** Vascular anatomy of the human flexor digitorum profundus tendon insertion. *J Hand Surg Am* 2002;27-5:806-12.
- 38. Astrom M, Westlin N.** Blood flow in the human Achilles tendon assessed by laser Doppler flowmetry. *J Orthop Res* 1994;12-2:246-52.
- 39. Lewis JS.** Rotator cuff tendinopathy. *Br J Sports Med* 2009;43-4:236-41.
- 40. Fallon J, Blevins FT, Vogel K, Trotter J.** Functional morphology of the supraspinatus tendon. *J Orthop Res* 2002;20-5:920-6.
- 41. Berenson MC, Blevins FT, Plaas AH, Vogel KG.** Proteoglycans of human rotator cuff tendons. *J Orthop Res* 1996;14-4:518-25.
- 42. Benjamin M, Evans EJ.** Fibrocartilage. *J Anat* 1990;171:1-15.
- 43. Benjamin M, Evans EJ, Copp L.** The histology of tendon attachments to bone in man. *J Anat* 1986;149:89-100.
- 44. Burkhart SS, Esch JC, Jolson RS.** The rotator crescent and rotator cable: an anatomic description of the shoulder's "suspension bridge". *Arthroscopy* 1993;9-6:611-6.
- 45. !!! INVALID CITATION !!! .**
- 46. Lehman C, Cuomo F, Kummer FJ, Zuckerman JD.** The incidence of full thickness rotator cuff tears in a large cadaveric population. *Bull Hosp Jt Dis* 1995;54-1:30-1.
- 47. Grant HJ, Arthur A, Pichora DR.** Evaluation of interventions for rotator cuff pathology: a systematic review. *J Hand Ther* 2004;17-2:274-99.
- 48. Tempelhof S, Rupp S, Seil R.** Age-related prevalence of rotator cuff tears in asymptomatic shoulders. *J Shoulder Elbow Surg* 1999;8-4:296-9.
- 49. Maffulli N, Khan KM, Puddu G.** Overuse tendon conditions: time to change a confusing terminology. *Arthroscopy* 1998;14-8:840-3.
- 50. Rees JD, Wilson AM, Wolman RL.** Current concepts in the management of tendon disorders. *Rheumatology (Oxford)* 2006;45-5:508-21.
- 51. van Dijk CN, van Sterkenburg MN, Wiegerinck JI, Karlsson J, Maffulli N.** Terminology for Achilles tendon related disorders. *Knee Surg Sports Traumatol Arthrosc* 2011;19-5:835-41.

- 52. Andres BM, Murrell GA.** Treatment of tendinopathy: what works, what does not, and what is on the horizon. *Clin Orthop Relat Res* 2008;466-7:1539-54.
- 53. Alfredson H, Forsgren S, Thorsen K, Lorentzon R.** In vivo microdialysis and immunohistochemical analyses of tendon tissue demonstrated high amounts of free glutamate and glutamate NMDAR1 receptors, but no signs of inflammation, in Jumper's knee. *J Orthop Res* 2001;19-5:881-6.
- 54. Alfredson H, Ljung BO, Thorsen K, Lorentzon R.** In vivo investigation of ECRB tendons with microdialysis technique--no signs of inflammation but high amounts of glutamate in tennis elbow. *Acta Orthop Scand* 2000;71-5:475-9.
- 55. Neer CS, 2nd.** Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. *J Bone Joint Surg Am* 1972;54-1:41-50.
- 56. Seitz AL, McClure PW, Finucane S, Boardman Iii ND, Michener LA.** Mechanisms of rotator cuff tendinopathy: Intrinsic, extrinsic, or both? *Clinical Biomechanics* 2011;26-1:1-12.
- 57. Balke M, Schmidt C, Dedy N, Banerjee M, Bouillon B, Liem D.** Correlation of acromial morphology with impingement syndrome and rotator cuff tears. *Acta Orthop* 2013;84-2:178-83.
- 58. Codman EA, Akerson IB.** The Pathology Associated with Rupture of the Supraspinatus Tendon. *Ann Surg* 1931;93-1:348-59.
- 59. Codman EA.** Complete rupture of the supraspinatus tendon. Operative treatment with report of two successful cases. 1911. *J Shoulder Elbow Surg* 2011;20-3:347-9.
- 60. Jozsa L, Kannus P.** Histopathological findings in spontaneous tendon ruptures. *Scand J Med Sci Sports* 1997;7-2:113-8.
- 61. Armstrong JR.** Excision of the acromion in treatment of the supraspinatus syndrome; report of 95 excisions. *J Bone Joint Surg Br* 1949;31B-3:436-42.
- 62. Bigliani LU, Ticker JB, Flatow EL, Soslowsky LJ, Mow VC.** The relationship of acromial architecture to rotator cuff disease. *Clin Sports Med* 1991;10-4:823-38.
- 63. Nicholson GP, Goodman DA, Flatow EL, Bigliani LU.** The acromion: morphologic condition and age-related changes. A study of 420 scapulas. *J Shoulder Elbow Surg* 1996;5-1:1-11.
- 64. Shah NN, Bayliss NC, Malcolm A.** Shape of the acromion: congenital or acquired--a macroscopic, radiographic, and microscopic study of acromion. *J Shoulder Elbow Surg* 2001;10-4:309-16.
- 65. Archambault JM, Wiley JP, Bray RC.** Exercise loading of tendons and the development of overuse injuries. A review of current literature. *Sports Med* 1995;20-2:77-89.
- 66. Arnoczky SP, Lavagnino M, Egerbacher M.** The mechanobiological aetiopathogenesis of tendinopathy: is it the over-stimulation or the under-stimulation of tendon cells? *Int J Exp Pathol* 2007;88-4:217-26.

- 67. Matthews TJ, Hand GC, Rees JL, Athanasou NA, Carr AJ.** Pathology of the torn rotator cuff tendon. Reduction in potential for repair as tear size increases. *J Bone Joint Surg Br* 2006;88-4:489-95.
- 68. Nove-Josserand L, Edwards TB, O'Connor DP, Walch G.** The acromiohumeral and coracohumeral intervals are abnormal in rotator cuff tears with muscular fatty degeneration. *Clin Orthop Relat Res* 2005-433:90-6.
- 69. Petersson CJ, Redlund-Johnell I.** The subacromial space in normal shoulder radiographs. *Acta Orthop Scand* 1984;55-1:57-8.
- 70. Saupe N, Pfirrmann CW, Schmid MR, Jost B, Werner CM, Zanetti M.** Association between rotator cuff abnormalities and reduced acromiohumeral distance. *AJR Am J Roentgenol* 2006;187-2:376-82.
- 71. Weiner DS, Macnab I.** Superior migration of the humeral head. A radiological aid in the diagnosis of tears of the rotator cuff. *J Bone Joint Surg Br* 1970;52-3:524-7.
- 72. Azzoni R, Cabitza P, Parrini M.** Sonographic evaluation of subacromial space. *Ultrasonics* 2004;42-1-9:683-7.
- 73. Cholewinski JJ, Kusz DJ, Wojciechowski P, Cielinski LS, Zoladz MP.** Ultrasound measurement of rotator cuff thickness and acromio-humeral distance in the diagnosis of subacromial impingement syndrome of the shoulder. *Knee Surg Sports Traumatol Arthrosc* 2008;16-4:408-14.
- 74. Desmeules F, Minville L, Riederer B, Cote CH, Fremont P.** Acromio-humeral distance variation measured by ultrasonography and its association with the outcome of rehabilitation for shoulder impingement syndrome. *Clin J Sport Med* 2004;14-4:197-205.
- 75. Graichen H, Bonel H, Stammberger T, Haubner M, Rohrer H, Englmeier KH, Reiser M, Eckstein F.** Three-dimensional analysis of the width of the subacromial space in healthy subjects and patients with impingement syndrome. *AJR Am J Roentgenol* 1999;172-4:1081-6.
- 76. Hebert LJ, Moffet H, Dufour M, Moisan C.** Acromiohumeral distance in a seated position in persons with impingement syndrome. *J Magn Reson Imaging* 2003;18-1:72-9.
- 77. Ellman H, Hanker G, Bayer M.** Repair of the rotator cuff. End-result study of factors influencing reconstruction. *J Bone Joint Surg Am* 1986;68-8:1136-44.
- 78. Norwood LA, Barrack R, Jacobson KE.** Clinical presentation of complete tears of the rotator cuff. *J Bone Joint Surg Am* 1989;71-4:499-505.
- 79. Allmann KH, Uhl M, Gufler H, Biebow N, Hauer MP, Kotter E, Reichelt A, Langer M.** Cine-MR imaging of the shoulder. *Acta Radiol* 1997;38-6:1043-6.
- 80. Edelson JG.** The 'hooked' acromion revisited. *J Bone Joint Surg Br* 1995;77-2:284-7.
- 81. Epstein RE, Schweitzer ME, Frieman BG, Fenlin JM, Jr., Mitchell DG.** Hooked acromion: prevalence on MR images of painful shoulders. *Radiology* 1993;187-2:479-81.

- 82. Farley TE, Neumann CH, Steinbach LS, Petersen SA.** The coracoacromial arch: MR evaluation and correlation with rotator cuff pathology. *Skeletal Radiol* 1994;23-8:641-5.
- 83. Bigliani LU, Morrison DS, April EW.** The morphology of the acromion and its relationship to rotator cuff tears. *Orthop Trans.* 1986;10:228.
- 84. Kitay GS, Iannotti JP, Williams GR, Haygood T, Kneeland BJ, Berlin J.** Roentgenographic assessment of acromial morphologic condition in rotator cuff impingement syndrome. *J Shoulder Elbow Surg* 1995;4-6:441-8.
- 85. Banas MP, Miller RJ, Totterman S.** Relationship between the lateral acromion angle and rotator cuff disease. *J Shoulder Elbow Surg* 1995;4-6:454-61.
- 86. Nyffeler RW, Werner CM, Sukthankar A, Schmid MR, Gerber C.** Association of a large lateral extension of the acromion with rotator cuff tears. *J Bone Joint Surg Am* 2006;88-4:800-5.
- 87. Toivonen DA, Tuite MJ, Orwin JF.** Acromial structure and tears of the rotator cuff. *J Shoulder Elbow Surg* 1995;4-5:376-83.
- 88. Vaz S, Soyer J, Pries P, Clarac JP.** Subacromial impingement: influence of coracoacromial arch geometry on shoulder function. *Joint Bone Spine* 2000;67-4:305-9.
- 89. Wang JC, Shapiro MS.** Changes in acromial morphology with age. *J Shoulder Elbow Surg* 1997;6-1:55-9.
- 90. Schippinger G, Bailey D, McNally EG, Kiss J, Carr AJ.** Anatomy of the normal acromion investigated using MRI. *Langenbecks Arch Chir* 1997;382-3:141-4.
- 91. MacGillivray JD, Fealy S, Potter HG, O'Brien SJ.** Multiplanar analysis of acromion morphology. *Am J Sports Med* 1998;26-6:836-40.
- 92. Ogawa K, Yoshida A, Inokuchi W, Naniwa T.** Acromial spur: relationship to aging and morphologic changes in the rotator cuff. *J Shoulder Elbow Surg* 2005;14-6:591-8.
- 93. Loehr J, Uthoff H.** The pathogenesis of degenerative rotator cuff tears. *Orthop Trans.* 1987;11:237-44.
- 94. Ogata S, Uthoff HK.** Acromial enthesopathy and rotator cuff tear. A radiologic and histologic postmortem investigation of the coracoacromial arch. *Clin Orthop Relat Res* 1990-254:39-48.
- 95. Chang EY, Moses DA, Babb JS, Schweitzer ME.** Shoulder impingement: objective 3D shape analysis of acromial morphologic features. *Radiology* 2006;239-2:497-505.
- 96. Chamblor AF, Pitsillides AA, Emery RJ.** Acromial spur formation in patients with rotator cuff tears. *J Shoulder Elbow Surg* 2003;12-4:314-21.
- 97. Ozaki J, Fujimoto S, Nakagawa Y, Masuhara K, Tamai S.** Tears of the rotator cuff of the shoulder associated with pathological changes in the acromion. A study in cadavera. *J Bone Joint Surg Am* 1988;70-8:1224-30.

- 98. Panni AS, Milano G, Lucania L, Fabbriani C, Logroscino CA.** Histological analysis of the coracoacromial arch: correlation between age-related changes and rotator cuff tears. *Arthroscopy* 1996;12-5:531-40.
- 99. Zuckerman JD, Kummer FJ, Cuomo F, Greller M.** Interobserver reliability of acromial morphology classification: an anatomic study. *J Shoulder Elbow Surg* 1997;6-3:286-7.
- 100. Peh WC, Farmer TH, Totty WG.** Acromial arch shape: assessment with MR imaging. *Radiology* 1995;195-2:501-5.
- 101. Bright AS, Torpey B, Magid D, Codd T, McFarland EG.** Reliability of radiographic evaluation for acromial morphology. *Skeletal Radiol* 1997;26-12:718-21.
- 102. Pedowitz RA, Yamaguchi K, Ahmad CS, Burks RT, Flatow EL, Green A, Wies JL, St Andre J, Boyer K, Iannotti JP, Miller BS, Tashjian R, Watters WC, 3rd, Weber K, Turkelson CM, Raymond L, Sluka P, McGowan R.** American Academy of Orthopaedic Surgeons Clinical Practice Guideline on: optimizing the management of rotator cuff problems. *J Bone Joint Surg Am* 2012;94-2:163-7.
- 103. Hallstrom E, Karrholm J.** Shoulder kinematics in 25 patients with impingement and 12 controls. *Clin Orthop Relat Res* 2006;448:22-7.
- 104. Keener JD, Wei AS, Kim HM, Steger-May K, Yamaguchi K.** Proximal humeral migration in shoulders with symptomatic and asymptomatic rotator cuff tears. *J Bone Joint Surg Am* 2009;91-6:1405-13.
- 105. Ludewig PM, Cook TM.** Translations of the humerus in persons with shoulder impingement symptoms. *J Orthop Sports Phys Ther* 2002;32-6:248-59.
- 106. Royer PJ, Kane EJ, Parks KE, Morrow JC, Moravec RR, Christie DS, Teyhen DS.** Fluoroscopic assessment of rotator cuff fatigue on glenohumeral arthrokinematics in shoulder impingement syndrome. *J Shoulder Elbow Surg* 2009;18-6:968-75.
- 107. Endo K, Ikata T, Katoh S, Takeda Y.** Radiographic assessment of scapular rotational tilt in chronic shoulder impingement syndrome. *J Orthop Sci* 2001;6-1:3-10.
- 108. Hebert LJ, Moffet H, McFadyen BJ, Dionne CE.** Scapular behavior in shoulder impingement syndrome. *Arch Phys Med Rehabil* 2002;83-1:60-9.
- 109. Ludewig PM, Cook TM.** Alterations in shoulder kinematics and associated muscle activity in people with symptoms of shoulder impingement. *Phys Ther* 2000;80-3:276-91.
- 110. Lee SB, Itoi E, O'Driscoll SW, An KN.** Contact geometry at the undersurface of the acromion with and without a rotator cuff tear. *Arthroscopy* 2001;17-4:365-72.
- 111. Yamamoto N, Muraki T, Sperling JW, Steinmann SP, Itoi E, Cofield RH, An KN.** Impingement mechanisms of the Neer and Hawkins signs. *J Shoulder Elbow Surg* 2009;18-6:942-7.

- 112. Cools AM, Witvrouw EE, Declercq GA, Vanderstraeten GG, Cambier DC.** Evaluation of isokinetic force production and associated muscle activity in the scapular rotators during a protraction-retraction movement in overhead athletes with impingement symptoms. *Br J Sports Med* 2004;38-1:64-8.
- 113. Gumina S, Di Giorgio G, Postacchini F, Postacchini R.** Subacromial space in adult patients with thoracic hyperkyphosis and in healthy volunteers. *Chir Organi Mov* 2008;91-2:93-6.
- 114. Davidson PA, Elattrache NS, Jobe CM, Jobe FW.** Rotator cuff and posterior-superior glenoid labrum injury associated with increased glenohumeral motion: a new site of impingement. *J Shoulder Elbow Surg* 1995;4-5:384-90.
- 115. Edelson G, Teitz C.** Internal impingement in the shoulder. *J Shoulder Elbow Surg* 2000;9-4:308-15.
- 116. Jobe CM.** Posterior superior glenoid impingement: expanded spectrum. *Arthroscopy* 1995;11-5:530-6.
- 117. Kibler WB.** The role of the scapula in athletic shoulder function. *Am J Sports Med* 1998;26-2:325-37.
- 118. Burkhart SS, Morgan CD, Kibler WB.** The disabled throwing shoulder: spectrum of pathology Part III: The SICK scapula, scapular dyskinesis, the kinetic chain, and rehabilitation. *Arthroscopy* 2003;19-6:641-61.
- 119. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M.** Histopathology of common tendinopathies. Update and implications for clinical management. *Sports Med* 1999;27-6:393-408.
- 120. Magra M, Maffulli N.** Matrix metalloproteases: a role in overuse tendinopathies. *Br J Sports Med* 2005;39-11:789-91.
- 121. Sano H, Ishii H, Trudel G, Uthoff HK.** Histologic evidence of degeneration at the insertion of 3 rotator cuff tendons: a comparative study with human cadaveric shoulders. *J Shoulder Elbow Surg* 1999;8-6:574-9.
- 122. Hashimoto T, Nobuhara K, Hamada T.** Pathologic evidence of degeneration as a primary cause of rotator cuff tear. *Clin Orthop Relat Res* 2003-415:111-20.
- 123. Langberg H, Olesen J, Skovgaard D, Kjaer M.** Age related blood flow around the Achilles tendon during exercise in humans. *Eur J Appl Physiol* 2001;84-3:246-8.
- 124. Milgrom C, Schaffler M, Gilbert S, van Holsbeeck M.** Rotator-cuff changes in asymptomatic adults. The effect of age, hand dominance and gender. *J Bone Joint Surg Br* 1995;77-2:296-8.
- 125. Sher JS, Uribe JW, Posada A, Murphy BJ, Zlatkin MB.** Abnormal findings on magnetic resonance images of asymptomatic shoulders. *J Bone Joint Surg Am* 1995;77-1:10-5.
- 126. Yamamoto A, Takagishi K, Osawa T, Yanagawa T, Nakajima D, Shitara H, Kobayashi T.** Prevalence and risk factors of a rotator cuff tear in the general population. *J Shoulder Elbow Surg* 2010;19-1:116-20.

- 127. Riley GP, Harrall RL, Constant CR, Chard MD, Cawston TE, Hazleman BL.** Glycosaminoglycans of human rotator cuff tendons: changes with age and in chronic rotator cuff tendinitis. *Ann Rheum Dis* 1994;53-6:367-76.
- 128. Kumagai J, Sarkar K, Uthoff HK.** The collagen types in the attachment zone of rotator cuff tendons in the elderly: an immunohistochemical study. *J Rheumatol* 1994;21-11:2096-100.
- 129. Longo UG, Franceschi F, Ruzzini L, Rabitti C, Morini S, Maffulli N, Denaro V.** Histopathology of the supraspinatus tendon in rotator cuff tears. *Am J Sports Med* 2008;36-3:533-8.
- 130. Astrom M.** Laser Doppler flowmetry in the assessment of tendon blood flow. *Scand J Med Sci Sports* 2000;10-6:365-7.
- 131. Funakoshi T, Iwasaki N, Kamishima T, Nishida M, Ito Y, Kondo M, Minami A.** In vivo visualization of vascular patterns of rotator cuff tears using contrast-enhanced ultrasound. *Am J Sports Med* 2010;38-12:2464-71.
- 132. Rudzki JR, Adler RS, Warren RF, Kadrmaz WR, Verma N, Pearle AD, Lyman S, Fealy S.** Contrast-enhanced ultrasound characterization of the vascularity of the rotator cuff tendon: age- and activity-related changes in the intact asymptomatic rotator cuff. *J Shoulder Elbow Surg* 2008;17-1 Suppl:96S-100S.
- 133. Fukuda H, Hamada K, Yamanaka K.** Pathology and pathogenesis of bursal-side rotator cuff tears viewed from en bloc histologic sections. *Clin Orthop Relat Res* 1990-254:75-80.
- 134. Goodmurphy CW, Osborn J, Akesson EJ, Johnson S, Stanescu V, Regan WD.** An immunocytochemical analysis of torn rotator cuff tendon taken at the time of repair. *J Shoulder Elbow Surg* 2003;12-4:368-74.
- 135. Biberthaler P, Wiedemann E, Nerlich A, Kettler M, Mussack T, Deckelmann S, Mutschler W.** Microcirculation associated with degenerative rotator cuff lesions. In vivo assessment with orthogonal polarization spectral imaging during arthroscopy of the shoulder. *J Bone Joint Surg Am* 2003;85-A-3:475-80.
- 136. Luo ZP, Hsu HC, Grabowski JJ, Morrey BF, An KN.** Mechanical environment associated with rotator cuff tears. *J Shoulder Elbow Surg* 1998;7-6:616-20.
- 137. Harvie P, Ostlere SJ, Teh J, McNally EG, Clipsham K, Burston BJ, Pollard TC, Carr AJ.** Genetic influences in the aetiology of tears of the rotator cuff. Sibling risk of a full-thickness tear. *J Bone Joint Surg Br* 2004;86-5:696-700.
- 138. Flynn RK, Pedersen CL, Birmingham TB, Kirkley A, Jackowski D, Fowler PJ.** The familial predisposition toward tearing the anterior cruciate ligament: a case control study. *Am J Sports Med* 2005;33-1:23-8.
- 139. Kannus P, Jarvinen TL, Jarvinen TA, Jarvinen M, Parkkari J, Khan K.** Painful Achilles tendon and its treatment. *Scand J Med Sci Sports* 2004;14-2:69-71.

- 140. Mokone GG, Gajjar M, September AV, Schwellnus MP, Greenberg J, Noakes TD, Collins M.** The guanine-thymine dinucleotide repeat polymorphism within the tenascin-C gene is associated with achilles tendon injuries. *Am J Sports Med* 2005;33-7:1016-21.
- 141. Mokone GG, Schwellnus MP, Noakes TD, Collins M.** The COL5A1 gene and Achilles tendon pathology. *Scand J Med Sci Sports* 2006;16-1:19-26.
- 142. Gotoh M, Hamada K, Yamakawa H, Inoue A, Fukuda H.** Increased substance P in subacromial bursa and shoulder pain in rotator cuff diseases. *J Orthop Res* 1998;16-5:618-21.
- 143. Bjur D, Danielson P, Alfredson H, Forsgren S.** Presence of a non-neuronal cholinergic system and occurrence of up- and down-regulation in expression of M2 muscarinic acetylcholine receptors: new aspects of importance regarding Achilles tendon tendinosis (tendinopathy). *Cell Tissue Res* 2008;331-2:385-400.
- 144. Danielson P, Alfredson H, Forsgren S.** Immunohistochemical and histochemical findings favoring the occurrence of autocrine/paracrine as well as nerve-related cholinergic effects in chronic painful patellar tendon tendinosis. *Microsc Res Tech* 2006;69-10:808-19.
- 145. Danielson P, Alfredson H, Forsgren S.** In situ hybridization studies confirming recent findings of the existence of a local nonneuronal catecholamine production in human patellar tendinosis. *Microsc Res Tech* 2007;70-10:908-11.
- 146. Danielson P, Alfredson H, Forsgren S.** Studies on the importance of sympathetic innervation, adrenergic receptors, and a possible local catecholamine production in the development of patellar tendinopathy (tendinosis) in man. *Microsc Res Tech* 2007;70-4:310-24.
- 147. Scott A, Alfredson H, Forsgren S.** VGlut2 expression in painful Achilles and patellar tendinosis: evidence of local glutamate release by tenocytes. *J Orthop Res* 2008;26-5:685-92.
- 148. Scott A, Lian O, Bahr R, Hart DA, Duronio V, Khan KM.** Increased mast cell numbers in human patellar tendinosis: correlation with symptom duration and vascular hyperplasia. *Br J Sports Med* 2008;42-9:753-7.
- 149. Abboud JA, Kim JS.** The effect of hypercholesterolemia on rotator cuff disease. *Clin Orthop Relat Res* 2010;468-6:1493-7.
- 150. Itoi E, Minagawa H, Konno N, Kobayashi T, Sato T, Sato K, Nishi T.** Relationship between smoking and rotator cuff tears. *Journal of Shoulder and Elbow Surgery*;5-2:S124.
- 151. Carbone S, Gumina S, Arceri V, Campagna V, Fagnani C, Postacchini F.** The impact of preoperative smoking habit on rotator cuff tear: cigarette smoking influences rotator cuff tear sizes. *J Shoulder Elbow Surg* 2012;21-1:56-60.

- 152. Galatz LM, Silva MJ, Rothermich SY, Zaegel MA, Havlioglu N, Thomopoulos S.** Nicotine delays tendon-to-bone healing in a rat shoulder model. *J Bone Joint Surg Am* 2006;88-9:2027-34.
- 153. Mallon WJ, Misamore G, Snead DS, Denton P.** The impact of preoperative smoking habits on the results of rotator cuff repair. *J Shoulder Elbow Surg* 2004;13-2:129-32.
- 154. Stenlund B, Goldie I, Hagberg M, Hogstedt C.** Shoulder tendinitis and its relation to heavy manual work and exposure to vibration. *Scand J Work Environ Health* 1993;19-1:43-9.
- 155. Chen AL, Shapiro JA, Ahn AK, Zuckerman JD, Cuomo F.** Rotator cuff repair in patients with type I diabetes mellitus. *J Shoulder Elbow Surg* 2003;12-5:416-21.
- 156. Reddy GK.** Glucose-mediated in vitro glycation modulates biomechanical integrity of the soft tissues but not hard tissues. *J Orthop Res* 2003;21-4:738-43.
- 157. Weiss JJ, Thompson GR, Doust V, Burgener F.** Rotator cuff tears in rheumatoid arthritis. *Archives of Internal Medicine* 1975;135-4:521-5.
- 158. Lin TW, Cardenas L, Soslowsky LJ.** Biomechanics of tendon injury and repair. *J Biomech* 2004;37-6:865-77.
- 159. Fukuda H.** The management of partial-thickness tears of the rotator cuff. *J Bone Joint Surg Br* 2003;85-1:3-11.
- 160. Matsen FA, 3rd.** Clinical practice. Rotator-cuff failure. *N Engl J Med* 2008;358-20:2138-47.
- 161. Yamaguchi K, Ditsios K, Middleton WD, Hildebolt CF, Galatz LM, Teefey SA.** The demographic and morphological features of rotator cuff disease. A comparison of asymptomatic and symptomatic shoulders. *J Bone Joint Surg Am* 2006;88-8:1699-704.
- 162. Lenza M, Buchbinder R, Takwoingi Y, Johnston RV, Hanchard NC, Faloppa F.** Magnetic resonance imaging, magnetic resonance arthrography and ultrasonography for assessing rotator cuff tears in people with shoulder pain for whom surgery is being considered. *Cochrane Database Syst Rev* 2013;9:CD009020.
- 163. Zanetti M, Hodler J.** Imaging of degenerative and posttraumatic disease in the shoulder joint with ultrasound. *Eur J Radiol* 2000;35-2:119-25.
- 164. Reilly P, Macleod I, Macfarlane R, Windley J, Emery RJ.** Dead men and radiologists don't lie: a review of cadaveric and radiological studies of rotator cuff tear prevalence. *Ann R Coll Surg Engl* 2006;88-2:116-21.
- 165. Hawkins RJ, Kennedy JC.** Impingement syndrome in athletes. *Am J Sports Med* 1980;8-3:151-8.
- 166. Jobe FW, Moynes DR.** Delineation of diagnostic criteria and a rehabilitation program for rotator cuff injuries. *Am J Sports Med* 1982;10-6:336-9.

- 167. Werner CM, Steinmann PA, Gilbert M, Gerber C.** Treatment of painful pseudoparesis due to irreparable rotator cuff dysfunction with the Delta III reverse-ball-and-socket total shoulder prosthesis. *J Bone Joint Surg Am* 2005;87-7:1476-86.
- 168. Nanda R, Gupta S, Kanapathipillai P, Liow RYL, Rangan A.** An assessment of the inter examiner reliability of clinical tests for subacromial impingement and rotator cuff integrity. *European Journal of Orthopaedic Surgery & Traumatology* 2008;18-7:495-500.
- 169. Walch G, Boulahia A, Calderone S, Robinson AH.** The 'dropping' and 'hornblower's' signs in evaluation of rotator-cuff tears. *J Bone Joint Surg Br* 1998;80-4:624-8.
- 170. Gerber C, Krushell RJ.** Isolated rupture of the tendon of the subscapularis muscle. Clinical features in 16 cases. *J Bone Joint Surg Br* 1991;73-3:389-94.
- 171. Gerber C, Hersche O, Farron A.** Isolated rupture of the subscapularis tendon. *J Bone Joint Surg Am* 1996;78-7:1015-23.
- 172. Hertel R, Ballmer FT, Lombert SM, Gerber C.** Lag signs in the diagnosis of rotator cuff rupture. *J Shoulder Elbow Surg* 1996;5-4:307-13.
- 173. Hughes PC, Taylor NF, Green RA.** Most clinical tests cannot accurately diagnose rotator cuff pathology: a systematic review. *Aust J Physiother* 2008;54-3:159-70.
- 174. Green R, Shanley K, Taylor NF, Perrott M.** The anatomical basis for clinical tests assessing musculoskeletal function of the shoulder. *Physical Therapy Reviews* 2008;13-1:17-24.
- 175. Hegedus EJ, Goode A, Campbell S, Morin A, Tamaddoni M, Moorman CT, 3rd, Cook C.** Physical examination tests of the shoulder: a systematic review with meta-analysis of individual tests. *Br J Sports Med* 2008;42-2:80-92; discussion
- 176. Calis M, Akgun K, Birtane M, Karacan I, Calis H, Tuzun F.** Diagnostic values of clinical diagnostic tests in subacromial impingement syndrome. *Ann Rheum Dis* 2000;59-1:44-7.
- 177. Hanchard NC, Lenza M, Handoll HH, Takwoingi Y.** Physical tests for shoulder impingements and local lesions of bursa, tendon or labrum that may accompany impingement. *Cochrane Database Syst Rev* 2013;4:CD007427.
- 178. Dinnes J, Loveman E, McIntyre L, Waugh N.** The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review. *Health Technol Assess* 2003;7-29:iii, 1-166.
- 179. Longo UG, Berton A, Ahrens PM, Maffulli N, Denaro V.** Clinical tests for the diagnosis of rotator cuff disease. *Sports Med Arthrosc* 2011;19-3:266-78.
- 180. Gupta R, Leggin BG, Iannotti JP.** Results of surgical repair of full-thickness tears of the rotator cuff. *Orthop Clin North Am* 1997;28-2:241-8.
- 181. Iannotti JP, Bernot MP, Kuhlman JR, Kelley MJ, Williams GR.** Postoperative assessment of shoulder function: a prospective study of full-thickness rotator cuff tears. *J Shoulder Elbow Surg* 1996;5-6:449-57.

- 182. Aleem AW, Brophy RH.** Outcomes of rotator cuff surgery: what does the evidence tell us? *Clin Sports Med* 2012;31-4:665-74.
- 183. Bryant L, Shnier R, Bryant C, Murrell GA.** A comparison of clinical estimation, ultrasonography, magnetic resonance imaging, and arthroscopy in determining the size of rotator cuff tears. *J Shoulder Elbow Surg* 2002;11-3:219-24.
- 184. de Jesus JO, Parker L, Frangos AJ, Nazarian LN.** Accuracy of MRI, MR arthrography, and ultrasound in the diagnosis of rotator cuff tears: a meta-analysis. *AJR Am J Roentgenol* 2009;192-6:1701-7.
- 185. Seltzer SE, Finberg HJ, Weissman BN, Kido DK, Collier BD.** Arthrosonography: gray-scale ultrasound evaluation of the shoulder. *Radiology* 1979;132-2:467-8.
- 186. Crass JR, Craig EV, Bretzke C, Feinberg SB.** Ultrasonography of the rotator cuff. *Radiographics* 1985;5-6:941-53.
- 187. Smith TO, Back T, Toms AP, Hing CB.** Diagnostic accuracy of ultrasound for rotator cuff tears in adults: A systematic review and meta-analysis. *Clin Radiol* 2011.
- 188. Recht MP, Resnick D.** Magnetic resonance-imaging studies of the shoulder. Diagnosis of lesions of the rotator cuff. *J Bone Joint Surg Am* 1993;75-8:1244-53.
- 189. Elentuck D, Palmer WE.** Direct magnetic resonance arthrography. *Eur Radiol* 2004;14-11:1956-67.
- 190. Hall FM, Rosenthal DI, Goldberg RP, Wyshak G.** Morbidity from shoulder arthrography: etiology, incidence, and prevention. *AJR Am J Roentgenol* 1981;136-1:59-62.
- 191. Balich SM, Sheley RC, Brown TR, Sauser DD, Quinn SF.** MR imaging of the rotator cuff tendon: interobserver agreement and analysis of interpretive errors. *Radiology* 1997;204-1:191-4.
- 192. Le Corroller T, Cohen M, Aswad R, Pauly V, Champsaur P.** Sonography of the painful shoulder: role of the operator's experience. *Skeletal Radiol* 2008;37-11:979-86.
- 193. O'Connor PJ, Grainger AJ, Morgan SR, Smith KL, Waterton JC, Nash AF.** Ultrasound assessment of tendons in asymptomatic volunteers: a study of reproducibility. *Eur Radiol* 2004;14-11:1968-73.
- 194. Robertson PL, Schweitzer ME, Mitchell DG, Schlesinger F, Epstein RE, Frieman BG, Fenlin JM.** Rotator cuff disorders: interobserver and intraobserver variation in diagnosis with MR imaging. *Radiology* 1995;194-3:831-5.
- 195. Chang CY, Wang SF, Chiou HJ, Ma HL, Sun YC, Wu HD.** Comparison of shoulder ultrasound and MR imaging in diagnosing full-thickness rotator cuff tears. *Clin Imaging* 2002;26-1:50-4.

- 196. Jacobson JA, Lancaster S, Prasad A, van Holsbeeck MT, Craig JG, Kolowich P.** Full-thickness and partial-thickness supraspinatus tendon tears: value of US signs in diagnosis. *Radiology* 2004;230-1:234-42.
- 197. Schibany N, Zehetgruber H, Kainberger F, Wurnig C, Ba-Ssalamah A, Herneth AM, Lang T, Gruber D, Breitenseher MJ.** Rotator cuff tears in asymptomatic individuals: a clinical and ultrasonographic screening study. *Eur J Radiol* 2004;51-3:263-8.
- 198. Berry H, Fernandes L, Bloom B, Clark RJ, Hamilton EB.** Clinical study comparing acupuncture, physiotherapy, injection and oral anti-inflammatory therapy in shoulder-cuff lesions. *Curr Med Res Opin* 1980;7-2:121-6.
- 199. Hawkins RJ, Plancher KD, Saddemi SR, Brezenoff LS, Moor JT.** Arthroscopic subacromial decompression. *J Shoulder Elbow Surg* 2001;10-3:225-30.
- 200. Littlewood C, Ashton J, Chance-Larsen K, May S, Sturrock B.** Exercise for rotator cuff tendinopathy: a systematic review. *Physiotherapy* 2012;98-2:101-9.
- 201. Buchbinder R, Green S, Youd JM.** Corticosteroid injections for shoulder pain. *Cochrane Database Syst Rev* 2003-1:CD004016.
- 202. Yamaguchi K, Tetro AM, Blam O, Evanoff BA, Teefey SA, Middleton WD.** Natural history of asymptomatic rotator cuff tears: a longitudinal analysis of asymptomatic tears detected sonographically. *J Shoulder Elbow Surg* 2001;10-3:199-203.
- 203. Mall NA, Kim HM, Keener JD, Steger-May K, Teefey SA, Middleton WD, Stobbs G, Yamaguchi K.** Symptomatic progression of asymptomatic rotator cuff tears: a prospective study of clinical and sonographic variables. *J Bone Joint Surg Am* 2010;92-16:2623-33.
- 204. Maman E, Harris C, White L, Tomlinson G, Shashank M, Boynton E.** Outcome of nonoperative treatment of symptomatic rotator cuff tears monitored by magnetic resonance imaging. *J Bone Joint Surg Am* 2009;91-8:1898-906.
- 205. Kuhn JE.** Exercise in the treatment of rotator cuff impingement: a systematic review and a synthesized evidence-based rehabilitation protocol. *J Shoulder Elbow Surg* 2009;18-1:138-60.
- 206. Desmeules F, Cote CH, Fremont P.** Therapeutic exercise and orthopedic manual therapy for impingement syndrome: a systematic review. *Clin J Sport Med* 2003;13-3:176-82.
- 207. Green S, Buchbinder R, Hetrick S.** Physiotherapy interventions for shoulder pain. *Cochrane Database Syst Rev* 2003-2:CD004258.
- 208. Marinko LN, Chacko JM, Dalton D, Chacko CC.** The effectiveness of therapeutic exercise for painful shoulder conditions: a meta-analysis. *J Shoulder Elbow Surg* 2011;20-8:1351-9.
- 209. Haahr JP, Andersen JH.** Exercises may be as efficient as subacromial decompression in patients with subacromial stage II impingement: 4-8 -

years' follow - up in a prospective, randomized study. *Scandinavian Journal of Rheumatology* 2006;35-3:224-8.

**210. Morrison DS, Frogameni AD, Woodworth P.** Non-operative treatment of subacromial impingement syndrome. *J Bone Joint Surg Am* 1997;79-5:732-7.

**211. Adebajo AO, Nash P, Hazleman BL.** A prospective double blind dummy placebo controlled study comparing triamcinolone hexacetonide injection with oral diclofenac 50 mg TDS in patients with rotator cuff tendinitis. *J Rheumatol* 1990;17-9:1207-10.

**212. White RH, Paull DM, Fleming KW.** Rotator cuff tendinitis: comparison of subacromial injection of a long acting corticosteroid versus oral indomethacin therapy. *J Rheumatol* 1986;13-3:608-13.

**213. van der Windt DA, van der Heijden GJ, Scholten RJ, Koes BW, Bouter LM.** The efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) for shoulder complaints. A systematic review. *J Clin Epidemiol* 1995;48-5:691-704.

**214. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C.** Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332-7553:1302-8.

**215. Itzkowitch D, Ginsberg F, Leon M, Bernard V, Appelboom T.** Peri-articular injection of tenoxicam for painful shoulders: a double-blind, placebo controlled trial. *Clin Rheumatol* 1996;15-6:604-9.

**216. Arroll B, Goodyear-Smith F.** Corticosteroid injections for painful shoulder: a meta-analysis. *Br J Gen Pract* 2005;55-512:224-8.

**217. Gray RG, Gottlieb NL.** Intra-articular corticosteroids. An updated assessment. *Clin Orthop Relat Res* 1983-177:235-63.

**218. van der Heijden GJ, van der Windt DA, Kleijnen J, Koes BW, Bouter LM.** Steroid injections for shoulder disorders: a systematic review of randomized clinical trials. *Br J Gen Pract* 1996;46-406:309-16.

**219. Halpern AA, Horowitz BG, Nagel DA.** Tendon ruptures associated with corticosteroid therapy. *West J Med* 1977;127-5:378-82.

**220. Kennedy JC, Willis RB.** The effects of local steroid injections on tendons: a biomechanical and microscopic correlative study. *Am J Sports Med* 1976;4-1:11-21.

**221. Oh LS, Wolf BR, Hall MP, Levy BA, Marx RG.** Indications for rotator cuff repair: a systematic review. *Clin Orthop Relat Res* 2007;455:52-63.

**222. Seida JC, LeBlanc C, Schouten JR, Mousavi SS, Hartling L, Vandermeer B, Tjosvold L, Sheps DM.** Systematic review: nonoperative and operative treatments for rotator cuff tears. *Ann Intern Med* 2010;153-4:246-55.

**223. Gartsman GM, Khan M, Hammerman SM.** Arthroscopic repair of full-thickness tears of the rotator cuff. *J Bone Joint Surg Am* 1998;80-6:832-40.

**224. Budoff JE, Nirschl RP, Guidi EJ.** Debridement of partial-thickness tears of the rotator cuff without acromioplasty. Long-term follow-up and review of the literature. *J Bone Joint Surg Am* 1998;80-5:733-48.

- 225. Ellman H, Kay SP.** Arthroscopic subacromial decompression for chronic impingement. Two- to five-year results. *J Bone Joint Surg Br* 1991;73-3:395-8.
- 226. Gebremariam L, Hay EM, Koes BW, Huisstede BM.** Effectiveness of surgical and postsurgical interventions for the subacromial impingement syndrome: a systematic review. *Arch Phys Med Rehabil* 2011;92-11:1900-13.
- 227. Tashjian RZ.** Is there evidence in favor of surgical interventions for the subacromial impingement syndrome? *Clin J Sport Med* 2013;23-5:406-7.
- 228. Caspari RB, Thal R.** A technique for arthroscopic subacromial decompression. *Arthroscopy* 1992;8-1:23-30.
- 229. Cordasco FA, Backer M, Craig EV, Klein D, Warren RF.** The partial-thickness rotator cuff tear: is acromioplasty without repair sufficient? *Am J Sports Med* 2002;30-2:257-60.
- 230. Liem D, Alci S, Dedy N, Steinbeck J, Marquardt B, Mollenhoff G.** Clinical and structural results of partial supraspinatus tears treated by subacromial decompression without repair. *Knee Surg Sports Traumatol Arthrosc* 2008;16-10:967-72.
- 231. Park JY, Yoo MJ, Kim MH.** Comparison of surgical outcome between bursal and articular partial thickness rotator cuff tears. *Orthopedics* 2003;26-4:387-90; discussion 90.
- 232. Chahal J, Mall N, MacDonald PB, Van Thiel G, Cole BJ, Romeo AA, Verma NN.** The role of subacromial decompression in patients undergoing arthroscopic repair of full-thickness tears of the rotator cuff: a systematic review and meta-analysis. *Arthroscopy* 2012;28-5:720-7.
- 233. Shin SJ, Oh JH, Chung SW, Song MH.** The efficacy of acromioplasty in the arthroscopic repair of small- to medium-sized rotator cuff tears without acromial spur: prospective comparative study. *Arthroscopy* 2012;28-5:628-35.
- 234. Gartsman GM, O'Connor D P.** Arthroscopic rotator cuff repair with and without arthroscopic subacromial decompression: a prospective, randomized study of one-year outcomes. *J Shoulder Elbow Surg* 2004;13-4:424-6.
- 235. Budoff JE, Rodin D, Ochiai D, Nirschl RP.** Arthroscopic rotator cuff debridement without decompression for the treatment of tendinosis. *Arthroscopy* 2005;21-9:1081-9.
- 236. Castagna A, Delle Rose G, Conti M, Snyder SJ, Borroni M, Garofalo R.** Predictive factors of subtle residual shoulder symptoms after transtendinous arthroscopic cuff repair: a clinical study. *Am J Sports Med* 2009;37-1:103-8.
- 237. Deutsch A.** Arthroscopic repair of partial-thickness tears of the rotator cuff. *J Shoulder Elbow Surg* 2007;16-2:193-201.
- 238. Kamath G, Galatz LM, Keener JD, Teefey S, Middleton W, Yamaguchi K.** Tendon integrity and functional outcome after arthroscopic repair of high-grade partial-thickness supraspinatus tears. *J Bone Joint Surg Am* 2009;91-5:1055-62.
- 239. Spencer EE, Jr.** Partial-thickness articular surface rotator cuff tears: an all-inside repair technique. *Clin Orthop Relat Res* 2010;468-6:1514-20.

- 240. Tauber M, Koller H, Resch H.** Transosseous arthroscopic repair of partial articular-surface supraspinatus tendon tears. *Knee Surg Sports Traumatol Arthrosc* 2008;16-6:608-13.
- 241. Strauss EJ, Salata MJ, Kercher J, Barker JU, McGill K, Bach BR, Jr., Romeo AA, Verma NN.** Multimedia article. The arthroscopic management of partial-thickness rotator cuff tears: a systematic review of the literature. *Arthroscopy* 2011;27-4:568-80.
- 242. Cofield RH, Parvizi J, Hoffmeyer PJ, Lanzer WL, Ilstrup DM, Rowland CM.** Surgical repair of chronic rotator cuff tears. A prospective long-term study. *J Bone Joint Surg Am* 2001;83-A-1:71-7.
- 243. Hawkins RJ, Misamore GW, Hobeika PE.** Surgery for full-thickness rotator-cuff tears. *J Bone Joint Surg Am* 1985;67-9:1349-55.
- 244. Baker CL, Liu SH.** Comparison of open and arthroscopically assisted rotator cuff repairs. *Am J Sports Med* 1995;23-1:99-104.
- 245. Levy HJ, Uribe JW, Delaney LG.** Arthroscopic assisted rotator cuff repair: preliminary results. *Arthroscopy* 1990;6-1:55-60.
- 246. Mohtadi NG, Hollinshead RM, Sasyniuk TM, Fletcher JA, Chan DS, Li FX.** A randomized clinical trial comparing open to arthroscopic acromioplasty with mini-open rotator cuff repair for full-thickness rotator cuff tears: disease-specific quality of life outcome at an average 2-year follow-up. *Am J Sports Med* 2008;36-6:1043-51.
- 247. Burkhart SS, Danaceau SM, Pearce CE, Jr.** Arthroscopic rotator cuff repair: Analysis of results by tear size and by repair technique-margin convergence versus direct tendon-to-bone repair. *Arthroscopy* 2001;17-9:905-12.
- 248. Morse K, Davis AD, Afra R, Kaye EK, Schepsis A, Voloshin I.** Arthroscopic versus mini-open rotator cuff repair: a comprehensive review and meta-analysis. *Am J Sports Med* 2008;36-9:1824-8.
- 249. Ide J, Maeda S, Takagi K.** A comparison of arthroscopic and open rotator cuff repair. *Arthroscopy* 2005;21-9:1090-8.
- 250. Lam F, Mok D.** Open repair of massive rotator cuff tears in patients aged sixty-five years or over: is it worthwhile? *J Shoulder Elbow Surg* 2004;13-5:517-21.
- 251. Worland RL, Arredondo J, Angles F, Lopez-Jimenez F.** Repair of massive rotator cuff tears in patients older than 70 years. *J Shoulder Elbow Surg* 1999;8-1:26-30.
- 252. Mather RC, 3rd, Koenig L, Acevedo D, Dall TM, Gallo P, Romeo A, Tongue J, Williams G, Jr.** The societal and economic value of rotator cuff repair. *J Bone Joint Surg Am* 2013;95-22:1993-2000.
- 253. Boileau P, Brassart N, Watkinson DJ, Carles M, Hatzidakis AM, Krishnan SG.** Arthroscopic repair of full-thickness tears of the supraspinatus: does the tendon really heal? *J Bone Joint Surg Am* 2005;87-6:1229-40.

- 254. Liem D, Bartl C, Lichtenberg S, Magosch P, Habermeyer P.** Clinical outcome and tendon integrity of arthroscopic versus mini-open supraspinatus tendon repair: a magnetic resonance imaging-controlled matched-pair analysis. *Arthroscopy* 2007;23-5:514-21.
- 255. Liem D, Lichtenberg S, Magosch P, Habermeyer P.** Magnetic resonance imaging of arthroscopic supraspinatus tendon repair. *J Bone Joint Surg Am* 2007;89-8:1770-6.
- 256. Sugaya H, Maeda K, Matsuki K, Moriishi J.** Functional and structural outcome after arthroscopic full-thickness rotator cuff repair: single-row versus dual-row fixation. *Arthroscopy* 2005;21-11:1307-16.
- 257. Sugaya H, Maeda K, Matsuki K, Moriishi J.** Repair integrity and functional outcome after arthroscopic double-row rotator cuff repair. A prospective outcome study. *J Bone Joint Surg Am* 2007;89-5:953-60.
- 258. Duquin TR, Buyea C, Bisson LJ.** Which method of rotator cuff repair leads to the highest rate of structural healing? A systematic review. *Am J Sports Med* 2010;38-4:835-41.
- 259. Isaac C, Gharaibeh B, Witt M, Wright VJ, Huard J.** Biologic approaches to enhance rotator cuff healing after injury. *J Shoulder Elbow Surg* 2012;21-2:181-90.
- 260. Bond JL, Dopirak RM, Higgins J, Burns J, Snyder SJ.** Arthroscopic replacement of massive, irreparable rotator cuff tears using a GraftJacket allograft: technique and preliminary results. *Arthroscopy* 2008;24-4:403-9 e1.
- 261. Pedowitz RA, Yamaguchi K, Ahmad CS, Burks RT, Flatow EL, Green A, Iannotti JP, Miller BS, Tashjian RZ, Watters WC, 3rd, Weber K, Turkelson CM, Wies JL, Anderson S, St Andre J, Boyer K, Raymond L, Sluka P, McGowan R, American Academy of Orthopaedic S.** Optimizing the management of rotator cuff problems. *J Am Acad Orthop Surg* 2011;19-6:368-79.
- 262. De Wilde L, Plasschaert F, Berghs B, Van Hoecke M, Verstraete K, Verdonk R.** Quantified measurement of subacromial impingement. *J Shoulder Elbow Surg* 2003;12-4:346-9.
- 263. Akgun K, Birtane M, Akarirmak U.** Is local subacromial corticosteroid injection beneficial in subacromial impingement syndrome? *Clin Rheumatol* 2004;23-6:496-500.
- 264. Hammond G.** Complete acromionectomy in the treatment of chronic tendinitis of the shoulder. A follow-up of ninety operations on eighty-seven patients. *J Bone Joint Surg Am* 1971;53-1:173-80.
- 265. Alvarez CM, Litchfield R, Jackowski D, Griffin S, Kirkley A.** A prospective, double-blind, randomized clinical trial comparing subacromial injection of betamethasone and xylocaine to xylocaine alone in chronic rotator cuff tendinosis. *Am J Sports Med* 2005;33-2:255-62.
- 266. Koester MC, Dunn WR, Kuhn JE, Spindler KP.** The efficacy of subacromial corticosteroid injection in the treatment of rotator cuff disease: A systematic review. *J Am Acad Orthop Surg* 2007;15-1:3-11.

- 267. Blair B, Rokito AS, Cuomo F, Jarolem K, Zuckerman JD.** Efficacy of injections of corticosteroids for subacromial impingement syndrome. *J Bone Joint Surg Am* 1996;78-11:1685-9.
- 268. Neustadt DH.** Local corticosteroid injection therapy in soft tissue rheumatic conditions of the hand and wrist. *Arthritis Rheum* 1991;34-7:923-6.
- 269. Cheng J, Abdi S.** Complications of Joint, Tendon, and Muscle Injections. *Tech Reg Anesth Pain Manag* 2007;11-3:141-7.
- 270. Hiemstra LA, Macdonald PB, Froese W.** Subacromial infection following corticosteroid injection. *J Shoulder Elbow Surg* 2003;12-1:91-3.
- 271. Green S, Buchbinder R, Glazier R, Forbes A.** Systematic review of randomised controlled trials of interventions for painful shoulder: selection criteria, outcome assessment, and efficacy. *BMJ* 1998;316-7128:354-60.
- 272. Petri M, Dobrow R, Neiman R, Whiting-O'Keefe Q, Seaman WE.** Randomized, double-blind, placebo-controlled study of the treatment of the painful shoulder. *Arthritis Rheum* 1987;30-9:1040-5.
- 273. Zheng XQ, Li K, Wei YD, Tie HT, Yi XY, Huang W.** Nonsteroidal anti-inflammatory drugs versus corticosteroid for treatment of shoulder pain: a systematic review and meta-analysis. *Arch Phys Med Rehabil* 2014;95-10:1824-31.
- 274. Jeunet F, Enz W, Guentert T.** Tenoxicam used as a parenteral formulation for acute pain in rheumatic conditions. *Scand J Rheumatol Suppl* 1989;80:59-61.
- 275. Jones RD, Miles W, Prankerd R, Lang C, Chilvers M, Lo SK.** Tenoxicam i.v. in major gynaecological surgery--pharmacokinetic, pain relief and haematological effects. *Anaesth Intensive Care* 2000;28-5:491-500.
- 276. Vischer TL.** Efficacy and tolerability of tenoxicam--an overview. *Eur J Rheumatol Inflamm* 1987;9-2:51-7.
- 277. Heintz RC, Guentert TW, Enrico JF, Dubach UC, Brandt R, Jeunet FS.** Pharmacokinetics of tenoxicam in healthy human volunteers. *Eur J Rheumatol Inflamm* 1984;7-2:33-44.
- 278. Colbert ST, Curran E, O'Hanlon DM, Moran R, McCarroll M.** Intra-articular tenoxicam improves postoperative analgesia in knee arthroscopy. *Can J Anaesth* 1999;46-7:653-7.
- 279. Cook TM, Tuckey JP, Nolan JP.** Analgesia after day-case knee arthroscopy: double-blind study of intra-articular tenoxicam, intra-articular bupivacaine and placebo. *Br J Anaesth* 1997;78-2:163-8.
- 280. Barnes PJ.** Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clin Sci (Lond)* 1998;94-6:557-72.
- 281. Rhen T, Cidlowski JA.** Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med* 2005;353-16:1711-23.
- 282. Krasner AS.** Glucocorticoid-induced adrenal insufficiency. *JAMA* 1999;282-7:671-6.

- 283. Lew KH, Ludwig EA, Milad MA, Donovan K, Middleton E, Jr., Ferry JJ, Jusko WJ.** Gender-based effects on methylprednisolone pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 1993;54-4:402-14.
- 284. Todd PA, Clissold SP.** Tenoxicam. An update of its pharmacology and therapeutic efficacy in rheumatic diseases. *Drugs* 1991;41-4:625-46.
- 285. Vane JR, Botting RM.** Mechanism of action of anti-inflammatory drugs. *Scand J Rheumatol Suppl* 1996;102:9-21.
- 286. Vane JR, Botting RM.** Mechanism of action of nonsteroidal anti-inflammatory drugs. *Am J Med* 1998;104-3A:2S-8S; discussion 21S-2S.
- 287. Whittle BJ, Higgs GA, Eakins KE, Moncada S, Vane JR.** Selective inhibition of prostaglandin production in inflammatory exudates and gastric mucosa. *Nature* 1980;284-5753:271-3.
- 288. Scaglione F, Demartini G, Dugnani S, Fraschini F, Triscari FA.** Pharmacokinetics of tenoxicam at different dosage regimes. *Farmaco* 1993;48-9:1321-5.
- 289. Constant CR, Murley AH.** A clinical method of functional assessment of the shoulder. *Clin Orthop* 1987-214:160-4.
- 290. Constant CR, Gerber C, Emery RJ, Sojbjerg JO, Gohlke F, Boileau P.** A review of the Constant score: modifications and guidelines for its use. *J Shoulder Elbow Surg* 2008;17-2:355-61.
- 291. Hudak PL, Amadio PC, Bombardier C.** Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). *Am J Ind Med* 1996;29-6:602-8.
- 292. Dawson J, Fitzpatrick R, Carr A.** Questionnaire on the perceptions of patients about shoulder surgery. *J Bone Joint Surg Br* 1996;78-4:593-600.
- 293. Beaton DE, Katz JN, Fossel AH, Wright JG, Tarasuk V, Bombardier C.** Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. *J Hand Ther* 2001;14-2:128-46.
- 294. Gummesson C, Atroshi I, Ekdahl C.** The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. *BMC Musculoskelet Disord* 2003;4:11.
- 295. Haahr JP, Ostergaard S, Dalsgaard J, Norup K, Frost P, Lausen S, Holm EA, Andersen JH.** Exercises versus arthroscopic decompression in patients with subacromial impingement: a randomised, controlled study in 90 cases with a one year follow up. *Ann Rheum Dis* 2005;64-5:760-4.
- 296. Henseler JF, Kolk A, van der Zwaal P, Nagels J, Vliet Vlieland TP, Nelissen RG.** The minimal detectable change of the Constant score in impingement, full-thickness tears, and massive rotator cuff tears. *J Shoulder Elbow Surg* 2015;24-3:376-81.

- 297. Kukkonen J, Kauko T, Vahlberg T, Joukainen A, Aarimaa V.** Investigating minimal clinically important difference for Constant score in patients undergoing rotator cuff surgery. *J Shoulder Elbow Surg* 2013;22-12:1650-5.
- 298. MacDonald PB, Clark P, Sutherland K.** An analysis of the diagnostic accuracy of the Hawkins and Neer subacromial impingement signs. *J Shoulder Elbow Surg* 2000;9-4:299-301.
- 299. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T.** The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134-8:663-94.
- 300. Moher D, Schulz KF, Altman DG.** The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357-9263:1191-4.
- 301. Nilsen OG.** Clinical pharmacokinetics of tenoxicam. *Clin Pharmacokinet* 1994;26-1:16-43.
- 302. Yoon SH, Lee HY, Lee HJ, Kwack KS.** Optimal dose of intra-articular corticosteroids for adhesive capsulitis: a randomized, triple-blind, placebo-controlled trial. *Am J Sports Med* 2013;41-5:1133-9.
- 303. Michener LA, McClure PW, Karduna AR.** Anatomical and biomechanical mechanisms of subacromial impingement syndrome. *Clin Biomech (Bristol, Avon)* 2003;18-5:369-79.
- 304. Bjorkenheim JM, Paavolainen P, Ahovuo J, Slati P.** Surgical repair of the rotator cuff and surrounding tissues. Factors influencing the results. *Clin Orthop Relat Res* 1988-236:148-53.
- 305. Watson M.** Major ruptures of the rotator cuff. The results of surgical repair in 89 patients. *J Bone Joint Surg Br* 1985;67-4:618-24.
- 306. Dogan N, Erdem AF, Gundogdu C, Kursad H, Kizilkaya M.** The effects of ketorolac and morphine on articular cartilage and synovium in the rabbit knee joint. *Can J Physiol Pharmacol* 2004;82-7:502-5.
- 307. Ozyuvaci H, Bilgic B, Ozyuvaci E, Altan A, Altug T, Karaca C.** Intra-articular injection of tenoxicam in rats: assessment of the local effects on the articular cartilage and synovium. *J Int Med Res* 2004;32-3:312-6.
- 308. Dingle JT.** The effects of NSAID on the matrix of human articular cartilages. *Z Rheumatol* 1999;58-3:125-9.
- 309. Radi ZA, Khan NK.** Effects of cyclooxygenase inhibition on bone, tendon, and ligament healing. *Inflamm Res* 2005;54-9:358-66.
- 310. Riley GP, Cox M, Harrall RL, Clements S, Hazleman BL.** Inhibition of tendon cell proliferation and matrix glycosaminoglycan synthesis by non-steroidal anti-inflammatory drugs in vitro. *J Hand Surg Br* 2001;26-3:224-8.
- 311. Cummins CA, Sasso LM, Nicholson D.** Impingement syndrome: temporal outcomes of nonoperative treatment. *J Shoulder Elbow Surg* 2009;18-2:172-7.
- 312. Gartsman GM.** Arthroscopic treatment of rotator cuff disease. *J Shoulder Elbow Surg* 1995;4-3:228-41.

- 313. Wu T, Song HX, Dong Y, Li JH.** Ultrasound-guided versus blind subacromial-subdeltoid bursa injection in adults with shoulder pain: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2015;45-3:374-8.
- 314. Yamakado K.** The targeting accuracy of subacromial injection to the shoulder: an arthrographic evaluation. *Arthroscopy* 2002;18-8:887-91.
- 315. Cole BF, Peters KS, Hackett L, Murrell GA.** Ultrasound-Guided Versus Blind Subacromial Corticosteroid Injections for Subacromial Impingement Syndrome: A Randomized, Double-Blind Clinical Trial. *Am J Sports Med* 2015.
- 316. Rutten MJ, Maresch BJ, Jager GJ, de Waal Malefijt MC.** Injection of the subacromial-subdeltoid bursa: blind or ultrasound-guided? *Acta Orthop* 2007;78-2:254-7.
- 317. Moosmayer S, Lund G, Seljom US, Haldorsen B, Svege IC, Hennig T, Pripp AH, Smith HJ.** Tendon repair compared with physiotherapy in the treatment of rotator cuff tears: a randomized controlled study in 103 cases with a five-year follow-up. *J Bone Joint Surg Am* 2014;96-18:1504-14.
- 318. Heffner HE, Heffner RS.** Hearing ranges of laboratory animals. *J Am Assoc Lab Anim Sci* 2007;46-1:20-2.
- 319. Takeda S, Morioka I, Miyashita K, Okumura A, Yoshida Y, Matsumoto K.** Age variation in the upper limit of hearing. *Eur J Appl Physiol Occup Physiol* 1992;65-5:403-8.
- 320. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, Wakefield RJ, Manger B, Working Group for Musculoskeletal Ultrasound in the ESCoICSiTT.** Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis* 2001;60-7:641-9.
- 321. Grassi W, Lamanna G, Farina A, Cervini C.** Sonographic imaging of normal and osteoarthritic cartilage. *Semin Arthritis Rheum* 1999;28-6:398-403.
- 322. Grassi W, Tittarelli E, Pirani O, Avaltroni D, Cervini C.** Ultrasound examination of metacarpophalangeal joints in rheumatoid arthritis. *Scand J Rheumatol* 1993;22-5:243-7.
- 323. Ihnatsenka B, Boezaart AP.** Ultrasound: Basic understanding and learning the language. *Int J Shoulder Surg* 2010;4-3:55-62.
- 324. Middleton WD, Reinus WR, Totty WG, Melson CL, Murphy WA.** Ultrasonographic evaluation of the rotator cuff and biceps tendon. *J Bone Joint Surg Am* 1986;68-3:440-50.
- 325. Wiener SN, Seitz WH, Jr.** Sonography of the shoulder in patients with tears of the rotator cuff: accuracy and value for selecting surgical options. *AJR Am J Roentgenol* 1993;160-1:103-7; discussion 9-10.
- 326. Teefey SA, Hasan SA, Middleton WD, Patel M, Wright RW, Yamaguchi K.** Ultrasonography of the rotator cuff. A comparison of ultrasonographic and arthroscopic findings in one hundred consecutive cases. *J Bone Joint Surg Am* 2000;82-4:498-504.

- 327. Huang LF, Rubin DA, Britton CA.** Greater tuberosity changes as revealed by radiography: lack of clinical usefulness in patients with rotator cuff disease. *AJR Am J Roentgenol* 1999;172-5:1381-8.
- 328. Wohlwend JR, van Holsbeeck M, Craig J, Shirazi K, Habra G, Jacobsen G, Bouffard JA.** The association between irregular greater tuberosities and rotator cuff tears: a sonographic study. *AJR Am J Roentgenol* 1998;171-1:229-33.
- 329. Arslan G, Apaydin A, Kabaalioglu A, Sindel T, Luleci E.** Sonographically detected subacromial/subdeltoid bursal effusion and biceps tendon sheath fluid: reliable signs of rotator cuff tear? *J Clin Ultrasound* 1999;27-6:335-9.
- 330. Hollister MS, Mack LA, Patten RM, Winter TC, 3rd, Matsen FA, 3rd, Veith RR.** Association of sonographically detected subacromial/subdeltoid bursal effusion and intraarticular fluid with rotator cuff tear. *AJR Am J Roentgenol* 1995;165-3:605-8.
- 331. Ziegler DW.** The use of in-office, orthopaedist-performed ultrasound of the shoulder to evaluate and manage rotator cuff disorders. *J Shoulder Elbow Surg* 2004;13-3:291-7.
- 332. Turrin A, Cappello A.** Sonographic anatomy of the supraspinatus tendon and adjacent structures. *Skeletal Radiol* 1997;26-2:89-93.
- 333. Gao X, Starmer J, Martin ER.** A multiple testing correction method for genetic association studies using correlated single nucleotide polymorphisms. *Genet Epidemiol* 2008;32-4:361-9.
- 334. Nyholt DR.** A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. *Am J Hum Genet* 2004;74-4:765-9.
- 335. Bland JM, Altman DG.** Multiple significance tests: the Bonferroni method. *BMJ* 1995;310-6973:170.
- 336. Ioannidis JP.** Why most published research findings are false. *PLoS Med* 2005;2-8:e124.
- 337. Rothman KJ.** No adjustments are needed for multiple comparisons. *Epidemiology* 1990;1-1:43-6.
- 338. Bender R, Lange S.** Adjusting for multiple testing--when and how? *J Clin Epidemiol* 2001;54-4:343-9.
- 339. Bland JM, Altman DG.** Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1-8476:307-10.
- 340. Cohen J.** *Statistical Power Analysis for the Behavioral Sciences*. 2nd edition ed. New Jersey: Lawrence Erlbaum, 1988.
- 341. Bland JM, Altman DG.** Applying the right statistics: analyses of measurement studies. *Ultrasound Obstet Gynecol* 2003;22-1:85-93.
- 342. Volk AG, Vangness CT, Jr.** An anatomic study of the supraspinatus muscle and tendon. *Clin Orthop Relat Res* 2001-384:280-5.

- 343. Kim SY, Boynton EL, Ravichandiran K, Fung LY, Bleakney R, Agur AM.** Three-dimensional study of the musculotendinous architecture of supraspinatus and its functional correlations. *Clin Anat* 2007;20-6:648-55.
- 344. Vahlensieck M, an Haack K, Schmidt HM.** Two portions of the supraspinatus muscle: a new finding about the muscles macroscopy by dissection and magnetic resonance imaging. *Surg Radiol Anat* 1994;16-1:101-4.
- 345. Itoi E, Hsu HC, Carmichael SW, Morrey BF, An KN.** Morphology of the torn rotator cuff. *J Anat* 1995;186 ( Pt 2):429-34.
- 346. Juul-Kristensen B, Bojsen-Moller F, Finsen L, Eriksson J, Johansson G, Stahlberg F, Ekdahl C.** Muscle sizes and moment arms of rotator cuff muscles determined by magnetic resonance imaging. *Cells Tissues Organs* 2000;167-2-3:214-22.
- 347. Akturk M, Karaahmetoglu S, Kacar M, Muftuoglu O.** Thickness of the supraspinatus and biceps tendons in diabetic patients. *Diabetes Care* 2002;25-2:408.
- 348. Jadoul M, Malghem J, Vande Berg B, van Ypersele de Strihou C.** Ultrasonographic detection of thickened joint capsules and tendons as marker of dialysis-related amyloidosis: a cross-sectional and longitudinal study. *Nephrol Dial Transplant* 1993;8-10:1104-9.
- 349. Bretzke CA, Crass JR, Craig EV, Feinberg SB.** Ultrasonography of the rotator cuff. Normal and pathologic anatomy. *Invest Radiol* 1985;20-3:311-5.
- 350. Wallny T, Wagner UA, Prange S, Schmitt O, Reich H.** Evaluation of chronic tears of the rotator cuff by ultrasound. A new index. *J Bone Joint Surg Br* 1999;81-4:675-8.
- 351. Wang HK, Lin JJ, Pan SL, Wang TG.** Sonographic evaluations in elite college baseball athletes. *Scand J Med Sci Sports* 2005;15-1:29-35.
- 352. Juul-Kristensen B, Bojsen-Moller F, Holst E, Ekdahl C.** Comparison of muscle sizes and moment arms of two rotator cuff muscles measured by ultrasonography and magnetic resonance imaging. *Eur J Ultrasound* 2000;11-3:161-73.
- 353. Katayose M, Magee DJ.** The cross-sectional area of supraspinatus as measured by diagnostic ultrasound. *J Bone Joint Surg Br* 2001;83-4:565-8.
- 354. Ellman H.** Diagnosis and treatment of incomplete rotator cuff tears. *Clin Orthop Relat Res* 1990-254:64-74.
- 355. Taggart A, Filippucci E, Wright G, Bell A, Cairns A, Meenagh G, Pendleton A, Rooney M, Wright S, Grey A, Grassi W.** Musculoskeletal ultrasound training in rheumatology: the Belfast experience. *Rheumatology (Oxford)* 2006;45-1:102-5.
- 356. Lindblom K.** On Pathogenesis of Ruptures of the Tendon Aponeurosis of the Shoulder Joint. *Acta Radiologica [Old Series]* 1939;20-6:563-77.

- 357. Brooks CH, Revell WJ, Heatley FW.** A quantitative histological study of the vascularity of the rotator cuff tendon. *J Bone Joint Surg Br* 1992;74-1:151-3.
- 358. Adler RS, Fealy S, Rudzki JR, Kadrmaz W, Verma NN, Pearle A, Lyman S, Warren RF.** Rotator cuff in asymptomatic volunteers: contrast-enhanced US depiction of intratendinous and peritendinous vascularity. *Radiology* 2008;248-3:954-61.
- 359. Oliva F, Zocchi L, Codispoti A, Candi E, Celi M, Melino G, Maffulli N, Tarantino U.** Transglutaminases expression in human supraspinatus tendon ruptures and in mouse tendons. *Biochem Biophys Res Commun* 2009;379-4:887-91.
- 360. Papakonstantinou MK, Pan WR, le Roux CM, Richardson MD.** Arterial supply of the tendinous rotator cuff insertions: an anatomical study. *ANZ J Surg* 2012;82-12:928-34.
- 361. Fredriksson I, Fors C, Johansson J.** Laser Doppler Flowmetry - a Theoretical Framework. *Department of Biomedical Engineering*. Linköping University, 2007.
- 362. Hoyer C, Sandermann J, Paludan JP, Pavar S, Petersen LJ.** Diagnostic accuracy of laser Doppler flowmetry versus strain gauge plethysmography for segmental pressure measurement. *J Vasc Surg* 2013;58-6:1563-70.
- 363. Petersen LJ, Zacho HD, Lyngholm AM, Arendt-Nielsen L.** Tissue viability imaging for assessment of pharmacologically induced vasodilation and vasoconstriction in human skin. *Microvasc Res* 2010;80-3:499-504.
- 364. Sonmez TT, Al-Sawaf O, Brandacher G, Kanzler I, Tuchscheerer N, Tohidnezhad M, Kanatas A, Knobe M, Fragoulis A, Tolba R, Mitchell D, Pufe T, Wruck CJ, Holzle F, Liehn EA.** A novel laser-Doppler flowmetry assisted murine model of acute hindlimb ischemia-reperfusion for free flap research. *PLoS One* 2013;8-6:e66498.
- 365. Sorensen H, Secher NH, Siebenmann C, Nielsen HB, Kohl-Bareis M, Lundby C, Rasmussen P.** Cutaneous vasoconstriction affects near-infrared spectroscopy determined cerebral oxygen saturation during administration of norepinephrine. *Anesthesiology* 2012;117-2:263-70.
- 366. Jacobs P, Kowatsch R.** Sterrad Sterilization System: a new technology for instrument sterilization. *Endosc Surg Allied Technol* 1993;1-1:57-8.
- 367. Kyi MS, Holton J, Ridgway GL.** Assessment of the efficacy of a low temperature hydrogen peroxide gas plasma sterilization system. *J Hosp Infect* 1995;31-4:275-84.
- 368. Dean BJ, Franklin SL, Murphy RJ, Javaid MK, Carr AJ.** Glucocorticoids induce specific ion-channel-mediated toxicity in human rotator cuff tendon: a mechanism underpinning the ultimately deleterious effect of steroid injection in tendinopathy? *Br J Sports Med* 2014;48-22:1620-6.
- 369. Dean BJ, Lostis E, Oakley T, Rombach I, Morrey ME, Carr AJ.** The risks and benefits of glucocorticoid treatment for tendinopathy: a systematic

review of the effects of local glucocorticoid on tendon. *Semin Arthritis Rheum* 2014;43-4:570-6.

**370. Min KS, St Pierre P, Ryan PM, Marchant BG, Wilson CJ, Arrington ED.** A double-blind randomized controlled trial comparing the effects of subacromial injection with corticosteroid versus NSAID in patients with shoulder impingement syndrome. *J Shoulder Elbow Surg* 2013;22-5:595-601.

**371. Kesikburun S, Tan AK, Yilmaz B, Yasar E, Yazicioglu K.** Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy: a randomized controlled trial with 1-year follow-up. *Am J Sports Med* 2013;41-11:2609-16.

**372. Scarpone M, Rabago D, Snell E, Demeo P, Ruppert K, Pritchard P, Arbogast G, Wilson JJ, Balzano JF.** Effectiveness of Platelet-rich Plasma Injection for Rotator Cuff Tendinopathy: A Prospective Open-label Study. *Glob Adv Health Med* 2013;2-2:26-31.

**373. Beard D, Rees J, Rombach I, Cooper C, Cook J, Merritt N, Gray A, Gwilym S, Judge A, Savulescu J, Moser J, Donovan J, Jepson M, Wilson C, Tracey I, Wartolowska K, Dean B, Carr A, Group CS.** The CSAW Study (Can Shoulder Arthroscopy Work?) - a placebo-controlled surgical intervention trial assessing the clinical and cost effectiveness of arthroscopic subacromial decompression for shoulder pain: study protocol for a randomised controlled trial. *Trials* 2015;16:210.

**374. Carr AJ, Cooper CD, Campbell MK, Rees JL, Moser J, Beard DJ, Fitzpatrick R, Gray A, Dawson J, Murphy J, Bruhn H, Cooper D, Ramsay CR.** Clinical effectiveness and cost-effectiveness of open and arthroscopic rotator cuff repair [the UK Rotator Cuff Surgery (UKUFF) randomised trial]. *Health Technol Assess* 2015;19-80:1-218.